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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS

TWENTY-SEVENTH SESSION

HELD AT ATLANTIC CITY

MAY 14 AND 15, 1912

VOLUME XXVII

PHILADELPHIA
PRINTED FOR THE ASSOCIATION
1912

NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

DORNAN, PRINTER
701-709 ARCH STREET
PHILADELPHIA

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ASSOCIATION OF AMERICAN PHYSICIANS

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S. J. MELTZER, M.D.
HENRY SEWALL, M.D.
GEORGE DOCK, M.D.
FRANCIS H. WILLIAMS, M.D.

REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS.
W. S. THAYER, M.D.

ALTERNATE REPRESENTATIVE.
THEODORE C. JANEWAY, M.D.

ASSOCIATION OF AMERICAN PHYSICIANS

OFFICERS FOR THE YEAR 1912-1913

PRESIDENT.

LEWELLYS F. BARKER, M.D.

VICE-PRESIDENT.

SIMON FLEXNER, M.D.

SECRETARY.

GEORGE M. KOBER, M.D.

RECORDER.

SOLOMON SOLIS COHEN, M.D.

TREASURER.

J. P. CROZER GRIFFITH, M.D.

COUNCILLORS.

S. J. MELTZER, M.D.
HENRY SEWALL, M.D.
GEORGE DOCK, M.D.
FRANCIS H. WILLIAMS, M.D.
ALEXANDER McPHEDRAN, M.D.

REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS.

W. S. THAYER, M.D.

ALTERNATE REPRESENTATIVE.

THEODORE C. JANEWAY, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME

Year.	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis Delafield.	.....	.....	James Tyson.	A. B. Ball.
1887.	S. Weir Mitchell.	Francis Minot. R. Palmer Howard.	J. T. Whittaker.	Geo. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard.	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.

MEMBERS

* Original Members.

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Station L, St. Charles Ave., Baltimore, Md.
1894. Adami, J. George, Pathological Laboratory, McGill University, Montreal, Canada.
1905. Adams, Samuel S., 1 Dupont Circle, Washington, D. C.
1896. Adler, Isaac, 22 East 62d St., New York.
1911. Anders, James M., 1605 Walnut St., Philadelphia.
1911. Ashford, Bailey K., U. S. Army, San Juan, P. R.
1905. Babcock, Robert H., 100 State St., Chicago.
1908. Baldwin, E. R., Saranac Lake, N. Y.
1899. Barker, L. F., 1035 North Calvert St., Baltimore, Maryland.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 335 East 22d St., Chicago.
1898. Blackader, A. D., 236 Mountain St., Montreal, Canada.
1901. Blumer, George, 204 York St., New Haven, Conn.
1892. Bolton, B. Meade, 54 Hammond Ct., Washington, D. C.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1898. Brannan, John W., 11 West 12th St., New York.
1904. Brown, Philip K., No. 2, 25th Ave., San Francisco, Cal.
1911. Brown, Lawrason, Saranac Lake, N. Y.
1899. Cabot, R. C., 190 Marlborough St., Boston.
1912. Camac, C. N. B., 108 E. 65th St., New York.
1908. Capps, Joseph A., 150 Michigan Ave., Chicago.
1889. Cary, Charles, 340 Delaware Ave., Buffalo, N. Y.
1907. Christian, Henry A., 252 Marlboro St., Boston.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.
1909. Cole, Rufus I., 65 East 77th St., New York.
1904. Collins, Joseph, 37 West 54th St., New York.
1908. Conner, Lewis A., 121 East 62d St., New York.
1906. Coplin, W. M. L., 606 South 48th St., Philadelphia.
1888. Dana, Charles L., 53 West 53d St., New York.
1893. Dock, George, 1806 Locust St., St. Louis, Missouri.

ELECTED

1904. Edsall, David L., 80 Marlborough St., Boston, Mass.
1901. Edwards, Arthur R., 100 State St., Chicago.
1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.
1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Fischel, W. E., 2647 Washington Ave., St. Louis.
*1886. Fitz, Reginald H., 18 Arlington St., Boston.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
*1886. Forchheimer, F., 160 West 9th St., Cincinnati, Ohio.
1908. Freeman, R. G., 211 West 57th St., New York.
1894. Fussell, M. Howard, 421 Lyceum Ave., Manayunk, Phila.
1903. Futcher, Thomas B., 3 West Franklin St., Baltimore.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1898. Herrick, James B., 200 Ashland Boulevard, Chicago.
1910. Hewlett, Albion W., 902 Baldwin Ave., Ann Arbor, Mich.
1900. Holt, L. E., 14 West 55th St., New York.
1911. Hoover, C. F., 702 Rose Building, Cleveland, Ohio.
1911. Howard, W. T., Western Reserve Univ., Cleveland, Ohio.
1911. Howland, John, 1806 Locust St., St. Louis, Missouri.
*1886. Hun, Henry, 149 Washington Ave., Albany, N. Y.
1907. Hunt, Reid, Hygienic Laboratory, cor. 25th and E Sts. N. W., Washington, D. C.
1901. Jackson, Henry, 380 Marlborough St., Boston.
1899. James, Walter B., 17 West 54th St., New York.
1908. Janeway, Theodore C., 36 West 40th St., New York.
1902. Joslin, E. P., 81 Bay State Road, Boston.
*1886. Kinnicutt, Francis P., 39 East 35th St., New York.
1901. Kinyoun, J. J., 1421 Clifton St., Washington, D. C.
1902. Kober, Geo. M., 1819 Q St. N. W., Washington, D. C.
1900. Koplik, Henry, 30 East 62d St., New York.
1895. Lafleur, Henri A., 251 Peel St., Montreal, Canada.
1906. Lambert, Samuel W., 130 East 35th St., New York.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
1910. Libman, E., 180 East 64th St., New York.

ELECTED

1912. Locke, Edwin A., 311 Beacon St., Boston.
1911. Loeb, Leo, Barnard Skin and Cancer Hospital, St. Louis.
1909. Longcope, Warfield T., 680 Madison Avenue, New York.
*1886. Longstreth, Morris, 1416 Spruce St., Philadelphia.
1910. Lord, Frederick T., 305 Beacon St., Boston.
1905. Macallum, A. B., University of Toronto, Toronto, Canada.
1902. MacCallum, W. G., 437 W. 59th St., New York.
1905. McCrae, Thomas, 1627 Spruce St., Philadelphia.
1891. McPhedran, A., 151 Bloor St., Toronto, Canada.
1898. Mallory, F. B., Department of Pathology, Harvard Medical School, Boston.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolf, Medical School, Johns Hopkins University Baltimore.
1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
1898. Mitchell, John K., 1730 Spruce St., Philadelphia.
1908. Moffitt, Herbert C., 240 Stockton St., San Francisco, Cal.
1901. Morse, John Lovett, 70 Bay State Road, Boston.
1891. Northrup, W. P., 57 East 79th St., New York.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., 1806 Locust St., St. Louis, Missouri.
1899. Park, Wm. H., 315 West 76th St., New York.
1904. Pearce, R. M., 2114 De Lancey Place, Philadelphia.
1898. Pfaff, Franz, 29 Gloucester St., Boston.
1909. Pratt, Joseph H., 317 Marlborough St., Boston.
1903. Preble, Robert B., 590 Dearborn Ave., Chicago.
1899. Prince, Morton, 458 Beacon St., Boston.
*1886. Prudden, T. Mitchell, 160 West 59th St., New York.
*1886. Putnam, James J., 106 Marlborough St., Boston.
1894. Rachford, B. K., 323 Broadway, Cincinnati.
1904. Richardson, Mark W., 145 State House, Boston.
1905. Riesman, David, 1715 Spruce St., Philadelphia.
1907. Rosenau, M. J., Department of Hygiene, Harvard Medical School, Boston, Mass.
1893. Rotch, T. M., 197 Commonwealth Ave., Boston.
1911. Rudolf, Robert D., 396 Bloor St., Toronto, Canada.
1911. Russell, Frederick F., Surgeon-General's Office, U. S. Army, Washington, D. C.
1898. Sachs, B., 135 Central Park, New York.

ELECTED

1908. Sailer, Joseph, 1830 Spruce St., Philadelphia.
1900. Sears, George G., 19 Marlborough St., Boston.
1900. Sewall, Henry, 1360 Vine St., Denver, Col.
1902. Sippy, B. W., 103 State St., Chicago.
*1886. Smith, A. A., 18 West 51st St., New York.
1892. Smith, Theobald B., South St., Forest Hills, Boston.
1907. Sollmann, Torald H., 4327 Superior Ave., Cleveland.
1898. Stengel, Alfred, 1728 Spruce St., Philadelphia.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1911. Strong, Richard, Manila, P. I.
1907. Taylor, A. E., University of Pennsylvania, Philadelphia.
1899. Thacher, J. S., 20 West 50th St., New York.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1889. Thompson, W. Gilman, 34 East 31st St., New York.
1889. Thomson, Wm. H., 23 East 47th St., New York.
1912. Tileston, Wilder, 308 Crown St., New Haven.
1889. Vaughan, Victor C., University of Michigan, Ann Arbor, Mich.
1898. Vickery, Herman F., 263 Beacon St., Boston.
1901. Warthin, Aldred S., University of Michigan, Ann Arbor, Mich.
1906. Weaver, George H., 1743 W. Harrison St., Chicago.
*1886. Welch, William H., 807 St. Paul St., Baltimore.
1898. Wesbrook, F. F., State Board of Health, Minneapolis, Minn.
1912. Wells, H. G., Sprague Memorial Institute, Chicago.
1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
1898. Withington, Charles F., 35 Bay State Road, Boston.

ASSOCIATE MEMBERS

ELECTED

1912. Anderson, John F., Public Health Service, Washington.
1911. Auer John, 13 West 121st St., New York.
1910. Boggs, Thomas R., 21 West Chase St., Baltimore.
1908. Brooks, Harlow, 44 West 9th St., New York.
1911. Brown, Thomas R., Johns Hopkins Med. School, Baltimore.
1908. Bunting, C. H., University of Wisconsin, Madison, Wis.
1908. Claytor, T. A., 1826 R. Street, N. W. Washington, D. C.
1911. Coleman, Warren, 58 West 55th St., New York.
1908. Da Costa, J. C., Jr., 1022 Spruce St., Philadelphia.
1909. Ford, William Webber, 1134 Cathedral St., Baltimore, Md.
1909. Friedenwald, Julius, 1013 North Charles St., Baltimore.
1911. Gay, Frederick P., University of California, Berkeley, Cal.
1908. Halsey, J. T., 602 Perrin Building, New Orleans.
1911. Howard, Campbell P., Iowa City.
1911. Klotz, Oşkar, University of Pittsburg, Pa.
1912. McCrae, John, 160 Metcalf St., Montreal.
1912. Norris, Geo. W., 1530 Locust St., Philadelphia.
1912. Stewart, Hugh A., 437 W. 59th St., New York.
1911. Taussig, Albert E., Metropolitan Building, St. Louis.
1908. Vaughan, V. C., Jr., 603 Washington Arcade, Detroit.
1910. Wadsworth, Augustus B., 114 West 55th St., New York.
1912. Whipple, Geo. H., Johns Hopkins University, Baltimore.
1912. Wilbur, Ray L., California and Webster Sts., San Francisco.
1909. Wood, Francis Carter, 437 West 59th St., New York.

HONORARY MEMBERS

* Original Members

Elected Active Member	Elected Honorary Member	
*1886.	1912.	Jacobi, A., 19 East 47th St., New York.
*1886.	1912.	Mitchell, S. Weir, 1524 Walnut St., Philadelphia.
*1886.	1912.	Osler, Wm., Oxford University, England.

EMERITUS MEMBERS

* Original Members.

Elected Active Member	Elected Emeritus Member	
*1886.	1887.	Billings, John S., Astor Library, Lafayette Place, New York.
1888.	1910.	Bridge, Norman, 217 S. Broadway, Los Angeles, Cal.
*1886.	1897.	Chew, Samuel C., 215 West Lanvale St., Baltimore.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
*1886.	1907.	Delafield, Francis A., 5 West 50th St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A., Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, Rush Medical College, Chicago.
*1886.	1908.	Henry, Frederick P., 114 S. 18th St., Philadelphia.
1890.	1902.	Hurd, H. M., Johns Hopkins Hospital, Baltimore.
1889.	1904.	Loving, Starling, 229 East State St., Columbus, Ohio.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
*1886.	1911.	Peabody, Geo. L., 57 West 38th St., New York.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Phila.

Elected Active Member	Elected Emeritus Member	
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.
*1886.	1907.	Sternberg, George M., 2005 Massachusetts Ave., N. W., Washington.
*1886.	1906.	Trudeau, Edward L., Saranac Lake, N. Y.
*1886.	1912.	Tyson, James, 1506 Spruce St., Philadelphia.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge.
*1886.	1912.	Ward, Samuel B., 281 State St., Albany.
*1886.	1911.	Wilkins, George, 899 Dorchester St., Montreal.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
*1886.	1908.	Wood, Horatio C., 4107 Chester Ave., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members.

Date of Election

*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
*1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
*1886. Folsom, Chas. F., Boston.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Aiken, S. C.
*1886. Graham, J. E., Toronto, Canada.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, E. Darwin, Jr., New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
1890. Latimer, Thomas S., Baltimore.

Date of Election.

*1886. Leidy, Joseph, Philadelphia.
*1886. Loomis, Alfred L., New York.
*1886. Lyman, Henry M., Chicago.
1890. MacDonnell, R. P., Montreal, Canada.
*1886. McBride, Thomas A., New York.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Spring, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
*1886. Whittaker, James T., Cincinnati.

ROYAL SOCIETY OF MEDICINE
26 MAR 1913

ASSOCIATION
OF
AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 15, 1912

Article I

Object and Name

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

Article II

Members

The number of active members shall be limited to one hundred and sixty. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Article III

Officers

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

Article IV

Duty of Officers

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V

Council

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate,

and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI

Meetings

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the Transactions as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

Article VII

Quorum

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

Article VIII

Election of Members

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting

of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

Article IX

Annual Dues

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

Article X

Amendments to the Constitution

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

TWENTY-SEVENTH ANNUAL MEETING

Held at Atlantic City, May 14 *and* 15, 1912

The following members were present at the meeting:

A. C. Abbott,
J. J. Abel,
J. G. Adami,
S. S. Adams,
I. Adler,
J. M. Anders,
J. Auer,
E. R. Baldwin,
L. F. Barker,
G. Blumer,
T. R. Boggs,
C. S. Bond,
J. W. Brannan,
H. Brooks,
R. C. Cabot,
C. N. B. Camac,
H. A. Christian,
S. S. Cohen,
R. I. Cole,
W. Coleman,
L. A. Conner,
W. M. L. Coplin,
G. Dock,
D. L. Edsall,
F. G. Finley,
R. H. Fitz,
R. G. Freeman,
J. Friedenwald,
M. H. Fussell,
T. B. Futcher,
C. L. Greene,
J. P. C. Griffith,
H. A. Hare,
J. B. Herrick,
A. W. Hewlett,
C. F. Hoover,
C. P. Howard,
H. Hun,
R. Hunt,
T. C. Janeway,
E. P. Joslin,
F. P. Kinnicutt,
J. J. Kinyoun,
O. Klotz,
G. M. Kober,
H. Koplik,
H. A. Lafleur,
S. W. Lambert,
M. J. Lewis,
E. Libman,
E. A. Locke,
W. T. Longcope,
F. T. Lord,
T. McCrae,
A. McPhedran,
S. J. Meltzer,
J. L. Miller,
H. C. Moffitt,
W. P. Northrup,
F. G. Novy,
E. L. Opie,
W. H. Park,
R. M. Pearce,
J. H. Pratt,
T. M. Prudden,
M. W. Richardson,
D. Riesman,
M. J. Rosenau,
R. D. Rudolf,
F. F. Russell,
B. Sachs,
J. Sailer,

H. Sewall,
A. Stengel,
A. E. Taussig,
A. E. Taylor,
J. S. Thacher,
W. S. Thayer,
W. Tileston,
H. F. Vickery,
A. B. Wadsworth,
W. H. Welch,
F. F. Wesbrook,
L. B. Wilson,
C. F. Withington,
F. C. Wood,

Tuesday, May 14.

Morning Session.—The Association was called to order at 10 A.M. by President Adami, who delivered the President's address.

The Treasurer read his annual report, which was referred to an auditing committee consisting of Doctors Hun and Northrup.

The Secretary presented the following recommendations from the Council:

Resolved, That for the ensuing year the annual dues shall be as follows: Salaried laboratory workers, $5.00; practitioners, $15.00; associate members, $7.50, and that the Transactions of the Association be furnished upon application to Emeritus Members at $4.00 per volume.

Upon motion of Dr. Sachs the recommendation of the Council was approved.

The Secretary reported that the Council recommends the adoption of the following amendment, which was submitted at the last annual meeting:

Resolved, That Article II of the Constitution be amended so as to read: The number of active members shall be limited to one hundred and sixty.

Resolved, That a By-Law be adopted to read as follows: This increased limit of membership of one hundred and sixty shall be attained by adding not more than five new members in any year, in addition to such as are elected to fill vacancies occurring in the usual ways, until the total membership reaches one hundred and sixty.

Henry A. Christian,
A. Jacobi,
W. T. Longcope,
Victor C. Vaughan,
Wm. H. Welch.

Upon motion of Dr. John W. Brannan the amendment was adopted.

Dr. Hun for the Auditing Committee reported that the accounts of the Treasurer had been examined and found to be correct.

Dr. S. Solis Cohen moved that the President's address be referred to the Council, with a request to consider and report upon his recommendations before adjournment. Carried.

Drs. Harlow Brooks and John Carroll presented "A Clinical Study of the Effects of Sleep and Rest on Blood Pressure," which was discussed by Drs. Janeway, Miller, Thayer, Cohen, Conner, Sewall, Dr. Brooks closing the discussion.

Dr. David L. Edsall read a paper entitled "Observations on the Effect of Various Forms of Respiration," which was discussed by Drs. Joslin, Hoover, and Barker, Dr. Edsall closing the discussion.

Dr. C. F. Hoover presented a communication entitled "The Study of Respired Air in a Case of Cyanosis without Dyspnea," which was discussed by Drs. Edsall, Meltzer, and Janeway, Dr. Hoover closing the discussion.

Dr. M. J. Rosenau read a paper entitled "Organic Matter in the Expired Breath, and its Significance," which was discussed by Dr. S. J. Meltzer, Dr. Rosenau closing the discussion.

Dr. Henry Sewall and Dr. S. B. Childs presented a paper entitled "A Comparison of Physical Signs and *X*-Ray Pictures of the Chest in Early Stages of Pulmonary Tuberculosis," which was discussed by Drs. Northrup, Koplik, and I. Adler, and the discussion was closed by Dr. Sewell.

Dr. David Riesman and Dr. John A. Kolmar presented "An Experimental Contribution to the Study of Pneumonia," which was discussed by Drs. Meltzer, Wadsworth, and Kinyoun, Dr. Riesman closing the discussion.

Dr. A. B. Wadsworth presented "An Experimental Study of Pneumococcus Infection," which was discussed by Drs. Cole, Meltzer, and Rosenau, Dr. Wadsworth closing the discussion.

Dr. Henry Koplik read a paper entitled "Forms of Septic Infection Following Operation on the Tonsils and Adenoids," which was discussed by Drs. Tyson, Sewall, Libman, Meltzer, and Brannan, Dr. Koplik closing the discussion.

Drs. Benedict and Joslin presented a "Study of the Metabolism in Diabetes," which was discussed by Dr. Taylor, Dr. Joslin closing the discussion.

Adjourned at 1.25 P.M.

Afternoon Session.—The Association was called to order by President Adami at 2.40 P.M.

Dr. John Auer read a paper entitled "An Effect of Digitalis and Digitalis-like Substances upon the Right Ventricular Muscle," which was not discussed.

Dr. James B. Herrick read a paper entitled "The Symptoms of Sudden Obstruction of the Coronary Arteries," which was discussed by Dr. Libman.

Dr. Eugene L. Opie read a paper entitled "The Production of Edema," which was discussed by Drs. Meltzer and Adami, Dr. Opie closing the discussion.

Dr. Joseph L. Miller read a paper entitled "Clinical Experience in the Drug Treatment of Edema," which was discussed by Drs. Hare, Kinnicutt, Janeway, Libman, Meltzer, Cohen, and Edsall, Dr. Miller closing.

Dr. Albert E. Taussig read a paper entitled "Permanent Heart Block in Auricular Fibrillation Following the Use of Digitalis," which was discussed by Drs. Hare, Meltzer, Tyson, Barker, and Dock, Dr. Taussig closing the discussion.

Dr. E. Libman read a paper entitled "Clinical and Pathological Observations on Subacute Bacterial Endocarditis," which was discussed by Drs. Brooks, Herrick, Dock, and McPhedran, Dr. Libman closing the discussion.

Dr. Oskar Klotz read a paper entitled "Acute Rheumatic Fever and the Arteries," which was not discussed.

Dr. L. F. Barker presented a communication illustrated by Lantern Slides "On the Clinical Analysis of Some Disturbances of the Autonomic Nervous System, with Comments upon the So-called Vagotonic and Sympathico-tonic States," which was discussed by Drs. Cohen, Wilson, and Meltzer, Dr. Barker closing the discussion.

Drs. A. W. Hewlett and J. G. Van Zwaluwenburg presented

a communication entitled "Studies on the Peripheral Pulse," illustrated by Lantern Slides which was not discussed.

Dr. E. Libman demonstrated for Dr. George Baehr Lantern Slides illustrating "The Glomerular Lesions in Subacute Bacterial Endocarditis," which was not discussed.

Adjourned at 5.30 P.M.

Wednesday, May 10.

Morning Session.—The Association was called to order by President Adami at 10.05 A.M.

The Secretary presented the following recommendations: The Council, acting upon a petition signed by forty members of the Association, suggesting the propriety of electing three of the oldest members of the Association to Honorary Membership, recommends that Drs. Abraham Jacobi, S. Weir Mitchell, and William Osler be elected. Upon motion of Dr. James Tyson seconded by Dr. Bond, the Secretary was directed to cast the unanimous vote of the Association for Drs. Abraham Jacobi, S. Weir Mitchell, and William Osler as Honorary Members of the Association.

The Council to whom were referred the recommendations of the President in his address recommends:

First. That the President be authorized to appoint a special committee for the purpose of coöperating with the George Washington Memorial Association in securing funds for the erection of a permanent home for the scientific societies in the city of Washington. Upon motion of Dr. Tyson the recommendations of the Council was approved and the President appointed as members of this committee Drs. Tyson, Fitz, and Kinnicutt.

Second. The Council recommends that a medal to be known as the "Medal of the Association of American Physicians," be awarded from time to time upon the recommendation of the Council, in recognition of notable achievement in the science and art of medicine; such recommendations to be made only on the unanimous vote of the Council and an affirmative vote of three-fourths of the members present in the business meeting shall be necessary to confirm the award. Upon motion of Dr. F. P. Kinnicutt this recommendation was unanimously adopted.

Third. The Council also recommends the appointment of a special committee by the President for the purpose of obtaining the endowment for an annual lectureship before the Association. Upon motion of Dr. Kinnicutt the recommendation was unanimously adopted, and President Adami appointed on the above Committee Drs. Welch, S. W. Lambert, and Alexander McPhedran.

The Association then proceeded to the election of officers, active members, and associate members, with the following result: *President,* Lewellys F. Barker; *Vice-President,* Simon Flexner; *Secretary,* George M. Kober; *Recorder,* S. Solis Cohen; *Treasurer,* J. P. Crozer Griffith; *Councillor,* Alexander McPhedran.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons, W. S. Thayer; *Alternate Representative,* Theodore C. Janeway.

Active Members: Dr. C. N. B. Camac, New York; Dr. Edwin A. Locke, Boston; Dr. Wilder Tileston, New Haven; Dr. H. G. Wells, Chicago; Dr. Louis B. Wilson, Rochester, Minn.

Associate Members: Dr. John F. Anderson, Washington; Dr. John McCrea, Montreal; Dr. George W. Norris, Philadelphia; Dr. Hugh A. Stewart, New York; Dr. George H. Whipple, Baltimore, and Dr. Ray L. Wilbur, San Francisco.

Dr. Lewis A. Conner read a paper entitled "A Contribution to the Symptomatology and Early Diagnosis of Thrombophlebitis," which was discussed by Drs. Kinnicutt, Libman, Thayer, McPhedran, Welch, Sachs, and Cohen, Dr. Conner closing the discussion.

Dr. Louis B. Wilson presented a communication entitled "A Note on Fatal Cases of Postoperative Embolism," which was discussed by Drs. Welch, Stengel, and Conner, Dr. Wilson closing the discussion.

Dr. R. M. Pearce presented "An Experimental Study of the Retention of Foreign Protein by the Kidney," which was discussed by Drs. Rosenau and Barker, Dr. Pearce closing the discussion.

Dr. Martin H. Fischer read a paper, by invitation, entitled "On the Principles of Treatment in Nephritis," which was discussed by Drs. Janeway, Meltzer, Taylor, Barker, and Tyson, Dr. Fischer closing the discussion.

Drs. Thomas R. Boggs and C. G. Guthrie presented a communication entitled "The So-called Bence-Jones Albumosuria: A Report of Three Cases with Notes on the Chemical Studies of Protein," which was not discussed.

Dr. Alfred F. Hess read a paper by invitation entitled "A Study of Pylorospasms and of the Duodenal Ferments in Infants by Means of a Simple Catheter," which was not discussed.

Dr. Julius Friedenwald read a paper entitled "Some Clinical Aspects observed in the Study of a Thousand Cases of Ulcer of the Stomach and Duodenum," which was discussed by Drs. C. P. Howard, Thayer, and Anders, Dr. Friedenwald closing the discussion.

Dr. J. M. Anders read a paper entitled "Stenosis of the Duodenum; a Statistical Study with the Report of a New Case," which was not discussed.

Drs. J. B. Leathes and H. L. Raper presented a paper entitled "On the Absorption of Fat from the Blood by the Liver, "which was not discussed.

Dr. Thomas McCrea read a paper entitled "Syphilis of the Liver," which was discussed by Drs. Dock, Fussell, Anders, and Janeway, Dr. McCrae closing the discussion.

Adjourned 1.30 P.M.

Afternoon Session.—The Association was called to order by President Adami at 2.35 P.M.

Dr. James B. Herrick read a paper entitled "Diabetes Insipidus," which was not discussed.

Dr. S. P. Beebe, by invitation, read a paper entitled "A Further Report Upon the Nature and Medical Treatment of Graves' Disease," which was discussed by Drs. Dock, and Wilson, Dr. Beebe closing the discussion.

Dr. George Dock read a paper entitled "Defective Development from Arthritis in Early Life," which was discussed by Drs. Herrick and Sachs.

Dr. Leslie H. Spooner, by invitation, read a paper entitled, "Anti-Typhoid Inoculation: Three Years' Experience With its Use in Training Schools for Nurses in Massachusetts," which

was discussed by Drs. Park, Russell, Fussell, and Richardson, Dr. Spooner closing the discussion.

Dr. A. C. Abbott read a paper prepared by Dr. John Anderson Johnston, by invitation, entitled "An Experimental Research on the Typhoid Carrier," which was discussed jointly with the succeeding paper.

Dr. J. W. Brannan read a paper entitled "Hospitals and Typhoid Carriers," which was discussed by Drs. Welch, Park, and Russell and the discussion was closed by Dr. Abbott.

Dr. Warren Coleman read a paper entitled "Weight Curves in Typhoid Fever," which was discussed by Drs. Sewall and Fussell, Dr. Coleman closing the discussion.

Dr. William H. Park read a paper entitled, "The Advantages and Disadvantages of the Intravenous, Intramuscular, and Subcutaneous Injections of Antitoxin, which was not discussed.

Drs. F. G. Finley and L. J. Rhea presented a paper entitled "A Case of Meningococcus Endocarditis and Septicemia with late Appearance of Meningeal Symptoms," which was not discussed.

Dr. F. G. Novy read a paper entitled "Immunity Against Trypanosomes," which was discussed by Dr. Adami, Dr. Novy closing the discussion.

Dr. Francis C. Wood read a paper entitled "Demonstration of Lesions of Nitric Oxide Posioning," which was not discussed.

The following papers were read by title:

"Two Cases of Tumor of the Spinal Cord, with Specimens," by Thomas A. Claytor.

"Secretory Processes in the Normal Kidney and in Kidneys on which Experimental Lesions Have been Produced" (by invitation), by T. G. Brodie.

"After Notes of a Case of Banti's Disease from Which the Spleen was Removed Four Years Ago," by A. D. Blackader.

"An Unusual Case of Aural Sepsis," by Francis P. Kinnicutt.

"Bismuth Poisoning with Report of Case," by R. C. Cabot.

"Nitrobenzol Poisoning with Report of Case," by S. S. Adams.

"On the Hemolytic Action of Salts of Fatty Acids" (by invitation), by J. B. Leathes and W. F. McPhedran.

"Further Studies on the Internal Function of the Pancreas in Carbohydrate Metabolism," by Joseph H. Pratt.

"Metabolism of Scurvy in the Adult," by L. Baumann and C. P. Howard.

Dr. Kober moved that a vote of thanks be extended to the President for the very excellent programme and the impartial manner in which he had presided, and also to the managers of the Marlborough-Blenheim for the courtesy extended to the Association in providing the hall and service. Carried.

Adjourned 4.45 P.M.

GEORGE M. KOBER,
Secretary

ADDRESS OF THE PRESIDENT

By J. GEORGE ADAMI, M.D.
MONTREAL, CANADA

Our Association has now completed the twenty-seventh year of its existence. From its very origin it has represented all that is best and most progressive in American medicine as distinct from American surgery, in medical science as apart from medical politics. With the latter we have as an association nothing to do. It is the advance of pure medicine and medical science that concerns us. We all have rightly regarded election to membership in this Association as a signal honor, as a mark of appreciation of services rendered in the cause of medical advance afforded by one's peers. Even though we are a democratic community, I do not hesitate to say that it is proper and fitting that there be a peerage of this order, a peerage not hereditary but of merit, a council of leaders, a Witanagemot. There is need for a body that sets a high standard of accomplishment. If only from the lower standard of personal achievement it is good, healthy, and broadening for the young physician to know that work well done will obtain recognition, not merely in his home city, but by a body which is above and beyond local and even national considerations. Such a body raises us above the provincial spirit. Even France, who so ruthlessly destroyed all tokens of monarchy and empire, retains its Académie de Médecine.

It may be objected that I take my position, and take the status of our Association too seriously. I do not think so. I know that twenty years ago when I came to America I even then looked upon the Association of American Physicians as the foremost medical body on this continent; reading over the list of members in the Transactions, I, a stranger, saw that it embodied the names of all those whose writings had already become familiar to me across the seas. I know that no individual honor or distinction that has come

to me has given me such deep-seated gratification as election to membership of this Association. I do not even except the supreme honor which has been conferred upon me of election to your Presidential chair, for mingled with my deep appreciation of this last honor is the feeling of distress that one who has done yeoman service in advancing American medicine, one who is an original member of the Association, had in his kindliness and modest shrinking from official responsibility, resigned from the Executive that I might step into his shoes. I have been unfeignedly thankful to Professor Prudden for other acts of great kindness, but not for this. He, not I, should be addressing you today. Nevertheless, just as I hailed my election to membership as a demonstration that science knows no boundaries, so now on behalf of my colleagues from across the border and on my own behalf I thank you for this compliment to Canada.

It may be objected further that the status of our Association twenty years ago was very different from what it is today; not that the Association has lowered its ideals, but that the tide of medical research has poured onward and upward in so extraordinary a manner that we have been unable to cope with its flood. Twenty years ago this Association embraced all, or practically all, the foremost physicians and pathologists of the North American continent. Today it does not. We must admit that this is true, but does that lessen the importance and influence of the Association? So long as we conscientiously appoint to our body the pick of aspirants to membership, so long as we honestly choose the leaders from among the leaders, so long shall we remain representative of the highest and best in medicine. It is, I hold, both wise and the highest degree politic to maintain, aye, and to raise the standard of admission to our ranks, and if at the same time we recognize the great increase in the number of those eligible by gradually and cautiously increasing our numbers—and this we have done—if also as a further precaution we appoint an intermediate grade of probationers from whom to elect to full membership—this also we have done in establishing the Associateship—then good rather than harm surely ensues. It is an honor for a physician to be a Fellow of the Royal Society, or a Member of the Académie de Médecine. It is compara-

tively little honor to be chosen to a society in which the conditions for election are lax, or the number of those appointed is, if not unlimited, at least singularly large. In the two bodies named, conditions for election are severe and the number of vacancies limited, so that election has become a worthy object of ambition; the hope of appointment has become a spur to higher efforts and serves to incite men "to scorn delights and live laborious days" whether in the hospital or in the laboratory, or both.

But if this be so, if our Association represents, and represents worthily, the best and highest in American medical science, it is timely to ask whether we, as an Association, are living up to our possibilities and our responsibilities. It is right that we should look this matter squarely in the face. What have we as an Association accomplished during the last twelve months, or the year before that, or the year before that? First and foremost, we have banded together and brought into our Association leading representatives of our profession in and from all the greater medical centres of the United States and Canada. It is this establishment of intimacy and community of interests in advancing our science which is far more important than the routine business of our annual meetings. In a second, and I hold a lower place, must be placed communications delivered at these annual meetings. Not that, saying this, I fail to recognize their high quality. That is so obvious that it is unnecessary to discuss; unnecessary also to refer to the number of papers which have become classic which have originally been delivered before this Association and have appeared in our TRANSACTIONS from Dr. Fitz's studies upon appendicitis in the first volume onward; to the value to those attending the meetings of these yearly reviews of the researches accomplished by and in the wards and laboratories of members of our body, or the value of the discussions upon these communications, even if of late years those discussions have been rendered painfully short by the overfilling of our program.

But when we have said this and have noted, first, the value to the individual and to the community of a society of the elect; secondly, the value of the communion of the elect, and thirdly, the scientific importance of our annual meetings, we are impelled to ask—is this

all? Is there nothing further that a body of this standing and potentiality accomplishes or can properly be asked to undertake? Frankly, I do not see that we accomplish much beyond this. I do see that we might accomplish more, and if the outer world, as I think we ought to expect, regards us as I think we ought to regard ourselves, then that outer world may justly complain that occupying a high position we are not utilizing our opportunities to the fullest.

To be honest, I believe that we stand at the parting of the ways. Only within the last few days one of our members—and one of the keenest and most constant attendants at these meetings—suggested to me that it might be propounded—he was very delicate—that the Association had not the commanding position that it used to hold, that with the rise of the Association of Pathologists and Bacteriologists, of the New York Society of Experimental Biology and Medicine, of the Biochemical Association, of the Society for the Advancement of Clinical Research, not to mention many others, we must be prepared to step down from our present position of influence.

It seems to me, gentlemen, that to take this view is logically to accept the attitude that we are a useless body, that these other organizations are performing better than we can the objects for which our Association was founded, that we are a fifth wheel and may as well drop off the coach and out of existence. Does this, I ask represent the general opinion of our members? Surely not. The other way, the other alternative, is to rise to the occasion and show that we recognize our leadership and the responsibilities involved therein.

It will immediately be asked what more is there that we can do? The very vastness of the North American continent makes it impossible that meetings be held more than once a year. We cannot, therefore, hope to be the channel of publication of all, or of the main bulk, of medical observations and investigations of the first order. This has to be freely admitted. For like reasons, we cannot contemplate the eventual possession of a home of our own with offices and hall of assembly. This still less, now that by the recent resolution it is only once in three years that we surely meet in

Washington. It might, however, be suggested that our Association take the initiative in approaching the other national medical societies of like constitution, and propose the purchase or rental of some building in which the archives of the various societies might be preserved. With the course of years, the time has come when the bulk and importance of those archives make it inadvisable that they remain in private hands.

We live in the age of trusts and combines, and while the amount of routine secretarial business of such an Association as ours is insufficient to demand the appointment of a permanent clerk, it is sufficient to be an onerous burden upon those members of our body who in their good-will, not to say enthusiasm, consent to occupy the posts of Secretary and Treasurer. The same is true regarding our companion associations. It is worth considering whether we could not take the lead in establishing a central office for the transaction of the routine official business of the various national societies. Nay, more, Washington is the national and natural centre for the working of national societies, and these deserve national recognition. There is no proper building set apart in Washington for the meeting of these societies, or, indeed, for that of the international congresses, which year by year are held there. To take the example I know best, the British government has set apart Burlington House for the home of the Royal Society, the Royal Academy, the Royal Geographical, Mathematical, and other societies. Is not the time ripe, and more than ripe, for us to approach the government and ask it to follow the example just given; ask it to establish a suite of assembly halls for the accommodation of national and international scientific assemblies, and to provide in connection with these a suite of offices to house the archives of the different national scientific associations. I would suggest that we take up this matter, communicate with our colleagues and arrange for a delegation to wait upon the government, urging the establishing of a national institution of this order.

This is a matter in which we could appropriately take a leading and influential part; are there any other directions in which we can show our recognition of our responsibility? There is one that occurs to me. Some few weeks ago there came into my hands a Senate

document—the volume of reports upon the uncinariasis campaign in Porto Rico—a volume recording in direct official language what has been accomplished toward the annihilation of a disease which for generations has made the inhabitants of a fertile tropical island a by-word to the rest of the world on account of their laziness, appalling incapacity, and helplessness; among whom anemia was easily at the head of all causes of death. It was a member of the army of occupation who discovered the cause of this anemia, a member of the medical service of the United States Army, one whom for his notable work I am glad to say we last year elected to our body. He was not satisfied merely to determine the cause of the widespread disease. In season and out of season he worked against much opposition until after some years he brought the local government to appoint a Commission of three to investigate the disease, to establish dispensaries and treat the miserable victims of the hookworm. What is more, he prevailed upon the home authorities to allow him to be nominated as head of the Commission. The result has been extraordinary. In the course of a few years, over 300,000 of the inhabitants of Porto Rico have been cured of the disease, or one-third of the inhabitants of that island. From being useless cumberers of the ground, they have been restored to health, vigor, and usefulness. I know no more triumphant result of modern hygiene save the work accomplished by the Yellow Fever commission under the late Walter Reed, again a member of our Association, in Cuba. But what means have we as a profession, what means have the inhabitants of the United States as a people to show a due appreciation of so notable an achievement? It was the same with the work of the Yellow Fever Commission. There was no adequate recognition here in America of that supreme conquest.

If the United States as a community has no proper provision for showing its approval of deeds of this nature, surely we, as a profession, can signalize our appreciation, and I would suggest that it would be fitting for us to found or establish an Association Medal to be given not necessarily yearly, but as occasion arises, to that man, who in the opinion of our body had made some advance of the first order in medicine. I am inclined to think that the honor

conferred upon the recipient would be greater were the presentation not strictly an annual event, and were it hedged around with severe conditions such as a unanimous vote of the Council.

Another method of signifying our appreciation of medical research would be by the foundation and endowment of an annual lectureship to be delivered at the meeting of the Association, again employing this as a means of honoring those who make notable advances in our subject. It ought to be a signal token of appreciation to be selected, either to receive the Medal of the Association, or to deliver the annual Lecture.

These, gentlemen, are suggestions; I feel assured that the Council will gladly receive other suggestions tending to maintain and increase the dignity and influence of our body. Let me repeat that with honor comes responsibility, and that as a body the responsibility rests upon us to lead in the appreciation and stimulation of medical advance.

What I have suggested means, I know, increased expenditure. May I in this connection hint that we have reached our twenty-eighth year and have become well established without receiving a single grant or bequest from any member or any well-wisher. Will no one follow the example of our great prototype Harvey, and either in his lifetime or by his will, or both, put aside certain funds for the use of this Association, even as Harvey did for the College of Physicians he loved so well. This, again, is a suggestion of means whereby the power of our body could be increased and its influence carried on to generations yet to be born.

It is the sad duty that falls to the President on these occasions to recall the names and good deeds of comrades who have fallen out of the ranks since our last assembly. Usually the President has to recite more than one name; today there is one only, but that notable, John Herr Musser. You will all be with me when I say that our body and American medicine in general could well have spared many men rather than this one, taken away as he has been in full career. A keen student and enthusiastic clinician, a tireless worker with wide interests, a cheery friend, beloved alike by his patients and his professional brethren, we mourn his untimely death.

A CLINICAL STUDY OF THE EFFECTS OF SLEEP AND REST ON BLOOD PRESSURE

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Numerous physiological researches on both man and the lower animals have shown that there is a marked fall in blood pressure during sleep. Tarchanoff[1] showed that a fall of aortic pressure of from 20 to 50 mm. Hg. took place in young dogs during the early stages of sleep, and Hull[2] noted a fall in the blood pressure of man after a rest of an hour or so succeeding a preliminary rise during exercise.

Leonard Hill,[3] although admitting that a fall in pressure took place, did not believe that this drop was any greater during sleep than that which has been demonstrated as a simple result of rest combined with the prone posture. Brush and Fayerweather,[4] however, showed definitely that this was not the case, but that the fall was concurrent with sleep and that it was much greater than the drop which sometimes, but not invariably, takes place simply from rest or on lying down.

Howell (text-book) brings out the important fact that the maximum fall occurs between one and two hours after sleep and that this same period corresponds to the time of the greatest auditory insensibility, as determined by Kohlschütter, Czerney, and by Morgenthal and Presbergen.

Our attention was first called to these physiological facts in the course of the study of a case of peculiar mental and spinal

[1] Arch. Ital. de Biologie, 1894, xxi, 318.
[2] Jour. Phys., vol. xxii, p. 19.
[3] Lancet, 1898, vol. i, p. 282.
[4] Am. Jour. Phys., 1901,v, 199.

phenomena, manifested in an instance of disturbed cerebrospinal circulation. Further investigation conducted on carefully selected cases showed that in each individual a more or less constant variation in the blood pressure occurred, depending apparently more on the time of the observation than on other factors. For example, we found that the night pressures, taken in groups of night sleepers, were almost invariably lower than the day pressures in the same individuals, but that conversely in night workers and day sleepers the finding was reversed. In the hope that a careful study of these conditions might lead to an understanding of the subject which might be utilized clinically, we then undertook quite an extensive study, after we had first verified on patients the correctness as applied to them, of the general physiological facts above cited.

All of our observations were made using the 12 cm. stiff leather arm cuff, and in most instances either the Janeway or the Sahli sphygmomanometers were employed. For obvious reasons the study was confined to the systolic pressure. In most instances observations on individuals or groups of cases were corrected or verified by subsequent repetition under as nearly as possible the same conditions. In so far as practical, neurotic individuals and such others as through personal peculiarities would be likely to confuse or complicate the main points of our study were avoided, and an effort was made to select such instances as would appear to apply most fittingly to the question immediately under discussion. Naturally it was found that phlegmatic subjects showed much less hourly variations, such as might be excited by psychic stimulation, for this reason neurotic subjects were avoided in so far as possible.

For convenience of study and purely from the clinical standpoint, we have divided our series of carefully observed cases into three classes: Those in which the systolic pressure lay within the range of the usual; 110 to below 170 mm. Hg.; those in which the pressure was less than the usual, that is, below 110 mm.; and those in which the pressure was above 170 mm. Hg., which class comprised the high-pressure class. In order that widely discordant results might not be reached from this division into more or less

arbitrary classes, excessive alterations in pressure were not included in our tabulated series, though special but entirely individual studies have been made in such instances. Thus, for example, the very low systolic pressure of 65 mm. in a case of salvarsan poisoning was not included, nor were two instances of systolic pressure of 300 and 310 mm. respectively included.

In each series a basis of comparison was established by taking the pressure in each case between 4 and 5 P.M., for, as we have shown, the time of the day at least in its relation to the rhythmic sleep is an important matter when one comes to comparatively estimate and particularly to value blood pressure.

Sixty-eight cases which showed medium pressures were studied. These gave an average basic afternoon pressure of 142.5 mm. Systolic reading taken between one and two hours after the night sleep showed an average drop of 24 mm. Hg. Three hours after the morning waking the pressure still showed an average depression of 12 mm., and from this time during the day the pressure gradually rose until the average afternoon level was again reached, between four and five o'clock.

Thirty instances of low pressure were similarly studied. The group showed an average systolic pressure of 100 mm. (the minimum case had a pressure of 80 mm.). Pressure determined within from one to two hours after primary sleep showed an average drop of 16.5 mm. The morning reading still showed an average depression of 6.7 mm., with a slow return to the general average of evening pressure.

Twenty-nine cases of high pressure with an average systolic reading of 204.5 and a maximum two cases of 250 mm. showed an average one to two hour drop of 44.8 mm. and a morning pressure of —22.8.

It is a noteworthy fact that the least drop in pressure took place in those patients who had an initial low pressure and the greatest fall in those with the highest systolic reading. Just as under physiological conditions the maximum fall occurs within two hours after falling asleep, with a subsequent slow rise culminating in the afternoon reading.

This tendency toward an increased fall as a result of primary

sleep in instances of high pressures is even more strikingly illustrated in several isolated observations on excessive pressures. That this fall is a definite attempt at conservation on the part of nature needs no very vivid imagination to conceive.

Observations conducted on these and other groups of selected cases indicate that the preliminary drop after sleep is a very rapid one and that the rise thereafter begins during sleep, very soon after the point of minimum pressure and extends up gradually through the remainder of the sleep period, to slowly rise during the day until the maximum pressure of the afternoon is reached. This is the course when patients are confined to bed, but when they are allowed to rise and go about the ward there is a sudden but rapid rise of a few mm. incident to getting up, after which the usual slow upward curve ensues, and except in this particular no essential difference between bed and ambulatory cases is demonstrable.

Although it might be reasonably inferred from the foregoing that a regular blood-pressure curve exists not only in normal but also in hyper- and subnormal cases, and while such is true of the average cases, many exceptions exist, especially in subjects markedly influenced by various psychic factors and especially as we have demonstrated, in cases of circulatory decompensation or in cases about to decompensate.

The marked effect of nervousness and apprehension in influencing the blood pressure curve has not, we believe, been overestimated by clinicians, and as before mentioned in our systematic groups we have attempted, so far as practicable, to eliminate those patients in whom this factor was likely to be a dominant one.

Gumprecht found a fall in the pressure of laboring men with readings between 160 and 200 mm., after rest in bed on their entrance into the hospital, and he attributes this drop to unaccustomed rest. Hensen, however, calls attention to the higher readings usual in patients of this class on the first day of their hospital residence.[1] We are inclined, from our studies, to agree with Hensen, for we have not found that rest *per se*, that is, physical rest, materially alters either hyper- or normal blood pressure,

[1] Quoted by Theodore Janeway, A Clinical Study of Blood Pressure.

although it exerts a profound elevating influence on the low pressures of exhaustion.

It is admittedly foreign to the nature and intent of this paper to enter into an attempt at physiological interpretation of the fall of blood pressure after sleep, but the subject is so alluring and admits of so very many interesting and possibly therapeutically important inferences that it is difficult to totally abstain in this direction. From a somewhat limited number of observations conducted alike on high, medium, and low-pressure cases it seems that the fall in pressure after sleep is much more pronounced after the customary regular or rhythmic sleep, be this night or day, while the drop which also occurs as a result of the sleep taken at irregular intervals is much less in degree and less abrupt in appearance, although we have some evidence to the effect that after profound physical exhaustion the drop in pressure which occurs with sleep is even more rapid, but it does not fall much if any below the accustomed level which we believe from these clinical cases to be an *individual period*, though quite classifiable with similar instances in the same type of persons.

That the drop is in some way directly connected with the phenomena of sleep is apparently suggested by the fact that in our groups, when the patients were not allowed to sleep the pronounced fall does not take place although a certain drop occurs perhaps as a result of posture or rest. Furthermore, when sleep is disturbed, as by disagreeable dreams, noise, or pain, although complete unconsciousness may be attained, the drop is not so pronounced. This fact may very likely account for the comparative exhaustion which is clinically observable in patients after a night of disturbed although unconscious sleep. This fact was especially suggested by one night's observations when the sleep in the general ward had been disturbed by the presence of a delirious patient. Records taken of previously studied patients, who despite the annoyance had become unconscious, showed a drop, but not to the accustomed degree.

Disturbance of patients during the first sleep delays but does not necessarily prevent the maximum fall in pressure, but frequent interruption of sleep does prevent it. When the maximum drop

has taken place before the patient wakes it does not recur that night no matter how sound the subsequent sleep may be.

As to whether this drop is occasioned by the sleep or whether it occurs as a rhythmic phenomena, independent of but concurrent with sleep, we do not as yet feel entirely prepared to speak, but we do not think from our studies that it is in any way concerned in the causation of sleep, for the fall appears subsequent to rather than preliminary to or concurrent with sound sleep. As some of our instances apparently show, sleep, sound and refreshing, at the usual time and apparently entirely physiological may occur without this drop, we are nevertheless convinced that in general the drop is a physiological necessity and that its degree is determined, in at least a general way, by the requisite rest and release from tension desirable from this individual standpoint.

The amount of night urinary secretion is no way dependent on the grade or degree of pressure drop so far as can be determined from these cases.

In an attempt to apply these observations to clinical utility we have endeavored to ascertain whether prolonged sleep causes a proportionate lowering of the pressure. Within an ordinary degree at least this does not appear to be the case, and attempts to secure even a temporarily lower twenty-four-hour pressure by prolonging or deepening the sleep were apparently without avail. Furthermore, we found that little difference existed in the total twenty-four-hour pressure whether the patient is confined to bed or is allowed to be up and about.

A special series of observations were conducted to determine whether the sleep drop might not be artificially increased in order to secure a lower pressure curve in concrete cases of high pressure. We were entirely without results in this direction, and in cases in which the drop and curve had been previously determined by the administration of potassium bromide in a dosage of as high as 120 grains the degree or persistence of the fall was not increased. The same lack of result was shown when chloral hydrate in a dosage of 50 grains per night was given, yet the drop and curve were not materially altered. From these and from other clinical observations we feel justified in the discouraging conclusion that this

fall cannot as yet be utilized to therapeutically lower the blood pressure, and that although its effect in high blood-pressure cases is more marked than that of any drug in medicinal doses, it cannot be used therapeutically. It may, however, be said parenthetically that the more we study this question of blood pressure the more we become persuaded to the conclusion that the often frantic efforts to lower high blood pressure are perhaps as harmful, if successful, as they are usually futile.

DISCUSSION

Dr. Theodore C. Janeway: Dr. Brooks' exceedingly interesting observations seem to me to bring up certain questions of interpretation. In the first place it is clear, I think, to all of us that the fall in systolic blood pressure is not at all synonymous with the fall in mean blood pressure. It unquestionably parallels, to a certain extent, the fall in mean blood pressure, but I should imagine that the excessive fall in the high-pressure cases obtained during sleep, corresponded to about the same fall in mean pressure as the slighter fall in his low and normal blood-pressure cases. It may be largely due to the diminished size of the pulse wave at the periphery during sleep. Of course, for practical purposes we must depend largely upon systolic blood-pressure readings, though with the modern method of auscultatory measurement of blood pressure a rough approximation of the diastolic becomes feasible for almost anyone. The results which Dr. Brooks has reported recall to me the studies of Brush and Fayerweather many years ago, the early drop during the first hours of sleep in their experiments being particularly marked. While Dr. Brooks does not feel that he has seen marked effects from rest, I feel quite sure that they occur, and I could produce a number of charts to show the surprising effects of simple rest, combined with the hospital diet, which one adopts in nephritic cases, in producing a steady fall in pressure during one or two weeks, apart from any other therapeutic procedures. Gumprecht called attention to this in laboring men. In a large number of patients with chronic nephritis one can always find some individuals in whom under treatment merely by rest and diet the pressure will drop from 190 or 200 down to perfectly normal figures, which are maintained until the patient gets up and about. Then the pressure rises somewhat, but never to the original figures during the period of stay in the hospital. Now to what extent the element of physical rest can be separated from the sleep element is questionable. The element of mental rest is, I think, a

rather important one in the sleep question. Not merely freedom from excitement, but freedom from actual mental tension, because one can, during any blood-pressure estimation, find that simple attention to the procedure on the part of the patient will raise the blood pressure. This is almost wholly a rise of systolic pressure. I think Dr. Brooks is too pessimistic about the therapeutic application. It suggests that one of our most important duties is to secure not merely sleep, but, as Dr. Brooks points out, normal rhythmic sleep at the proper time as a means of safeguarding the heart.

Dr. Joseph Miller: Regarding Dr. Brooks' paper and the statements made by Dr. Janeway, it seems to me that the question of mental rest is in many instances quite as important as physical rest. In considering the effect of any form of treatment, we must bear in mind that the patients with high blood pressure often show very marked variations from day to day, quite independent of any form of treatment; such variations may reach 40, 60, or even 100 mm. These patients with high blood pressure, when they develop a hemiplegia, especially if this is followed by mental apathy, often have for many months a much lower blood pressure when in this mental state than they had previously shown; they are now free from all sorts of mental disturbances, such as worry, and this apparently has a decided effect on their blood pressure. I had such a patient under my observation who previous to her cerebral hemorrhage had a blood pressure of 180 to 190, and for a year following this rarely had a blood pressure above 150, often 130 and often 140. Her mental state was such that only extreme excitement had any effect upon her. When certain family disturbances developed (which occasionally did), her pressure would again go up temporarily for a day or two to 180 or 190.

Dr. W. S. Thayer: I also have often seen a striking reduction of the blood pressure in association with simple and continued rest in bed.

In connection with Dr. Brooks' observations as to the possible ill effects of too vigorous attempts to reduce pressure by drugs, I observed, several years ago, an interesting case.

A man consulted a colleague because of severe headache. There were evidences of chronic nephritis with a blood pressure of about 220 mm. Under vigorous treatment with nitrites the patient became anuric and comatose.

Return of the urinary secretion and recovery from the uremia occurred in association with a rise in the blood pressure to a point between 190 and 200.

Dr. S. Solis Cohen: I can confirm Dr. Brooks' observation that in the vast majority of cases carefully studied under such hospital conditions

as I have in Philadelphia, the abnormally high pressures are not materially affected by prolonged rest in bed. In a group of such cases under observation at the present time that fact has been particularly borne in upon me. Occasionally we find patients who show some marked effect, but usually the decline is small. On the other hand, we do find elevation of pressure from rest in cases of exhaustion. But the point that has chiefly impressed me has been the sudden, and for the time inexplicable, variations in the brachial pressure that occur in some patients in the course of a day while at continuous rest. Pressure changes of 20 to 30 points may thus be observed, and I have not yet been able to make out the cause. It is not emotion or diet. In some cases there is a uniform fall a short time after eating, continuing for an hour or two.

Dr. Lewis A. Conner: In continuing the discussion I shall have to endorse very emphatically the statement of Dr. Janeway and Dr. Thayer. One of the most distinct therapeutic results that we see is the beneficial effect, in cases of chronic hypertension, of rest in bed. I should say that in most of the cases I have observed that effect has been very obvious, and often it is very pronounced. Whether it is entirely the bodily rest or whether it is partly the effect of mental rest and quiet is perhaps a question, but I cannot believe that the effect upon the mind is the only factor concerned.

Dr. Henry Sewall: It seems to me we ought, as far as possible, find what rest really means as affecting tension. To my mind worry may be looked on as a poison which, in cases of delicate heart, does more damage than anything else; and I have seen such obvious effects of exalted arterial tension, with succeeding heart failure, dependent upon the mental attitude of the patient, particularly in women aged over sixty years, that I think we ought carefully to take into account that rest means not only rest of muscles, but rest of those nerve cells on whose well-being content, cheerfulness, and peace of mind depend.

Dr. Brooks: I feel very keenly the importance of this question of rest in hypertension cases. Rest may produce, as we all know, a lowering of blood pressure in such instances. I have taken some cases which showed improvement on rest in bed, put them out of doors and about their ordinary avocation; but given them freedom from worry and mental strain, and the same fall takes place. Conversely, patients who do not improve under mental or psychic relaxation fail to do so under merely physical methods. I do not then believe it is a question of physical rest which is most important, but one of mental rest. The psychic rest is the thing, and the term rest should be used in its broadest sense in therapeutics as in

definition. If a man is worrying about his business his pressure will not come down irrespective of physical measures. If he is relieved of business or social worries his pressure will come down whether he is in bed or not. Just a word as to the auscultatory determination of blood pressure. We found that this method of determining is very inaccurate, especially in certain conditions; and under ordinary circumstances we believe that the older method is far more reliable.

ORGANIC MATTER IN THE EXPIRED BREATH[1]

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(From the Department of Preventive Medicine and Hygiene, Harvard)

The presence of organic matter in the expired breath has long been suspected but never demonstrated. These substances have eluded chemical tests; and animal experimentation has heretofore furnished contradictory and inconclusive evidence. We here present results which we believe demonstrate that the expired breath contains organic matter and that this organic matter is specific in nature.

In the early experiments of Claude Bernard (1857) animals were confined in atmospheric air and in mixtures both richer and poorer in oxygen than atmospheric air. He explained the poisonous effects of carbonic acid when respired to be due to the fact that it deprived the animal of oxygen. Similar results were reported by Valentin and by Paul Bert. Richardson in 1860–61 found that a temperature much higher or lower than 20° C. had the effect of shortening very considerably the lives of animals confined in an unventilated jar. Pettenkoffer shortly thereafter (1860 to 1863) believed that the symptoms observed in crowded ill-ventilated places were not produced by the excess of carbonic acid nor by a decrease in the proportion of oxygen in the air. He further did not believe that the impure air of dwellings was directly capable of originating specific diseases or that it was really a poison in the ordinary sense of the term, but that it diminished the resistance on the part of those continually breathing such air.

The animals exposed by Brown-Séquard to the expired breath of other animals died, and he believed they died as a result of

[1] Illustrations from the Journal of Medical Research, vol. xxv, No. 1 (new series, vol. xx, No. 1), September, 1911.

poisonous matters in the expired breath. Whether these poisons were of organic nature or not could only be surmised; in fact, their very presence was vigorously denied by Billings, Mitchell, Bergey, and others who repeated Brown-Séquard's experiments with contradictory results. The ill effects from breathing air contaminated with the expired breath is now generally assumed to be due to the increased temperature and moisture rather than to the poisons which have so long been suspected and sometimes taken for granted. Thus Benedict[1] has kept persons in his calorimeter breathing and rebreathing the same air with a CO_2 content as high as 2 per cent. for twenty-four hours without discomfort, the only precaution being to keep the temperature down and to remove the moisture. It is to be noted that in these experiments some of the air was passed over lime and sulphuric acid every two hours, and the greater part of the moisture was removed by condensation, which may also remove other substances than the carbonic acid and moisture.

One of the notable achievements of bacteriology was to show that the expired breath during normal quiet respiration is practically sterile. The moist mucous membranes of the upper respiratory passages act as a bacterial trap. Before this demonstration it was assumed, and commonly believed, that many of the communicable diseases were transmitted from person to person through specific poisons contained in the expired breath. The fact that the expired breath usually contains no bacteria robbed it of much of the horror with which it had long been regarded. When science demonstrated that the expired breath was not particularly dangerous so far as the specific viruses of the communicable diseases are concerned it was entirely acquitted and given a free bill of health in the minds of many sanitarians. Flügge's demonstration of droplet infection and its possibilities partly restored the expired breath to a position of possible danger.

Our changing views toward the dangers in the air are well illustrated by the attitude of the surgeon. At first Lister and his followers in antiseptic surgery attempted to sterilize the air coming in contact with the wound. The work of Pasteur, Tyndall, and others had fostered the belief that the air was full of dangerous bacteria.

[1] Bulletin 175, Office of Experiment Stations, U. S. Dept. Agric., p. 235.

The surgeon now largely disregards the air of a well-appointed surgical clinic. He, however, ties pieces of sterile gauze about his mouth and nose and over his hair to prevent contamination by these sources.

Since it has been shown that the air under ordinary circumstances is not usually the vehicle by which the communicable diseases and the infections are conveyed, the pendulum has swung to the other extreme, especially as no harmful substances of a chemical nature could be demonstrated in the expired breath. The common experience that a vitiated atmosphere is harmful has recently been explained by its increase in temperature and increase in humidity. Some sanitarians have gone so far as to state that if the temperature and moisture can be kept down and the air kept in motion, say by an electric fan, it may be rebreathed. To this view we cannot subscribe, for we have always felt that a vitiated air must contain substances which are harmful even though not demonstrable to science. This question of ventilation is somewhat foreign though closely related to our present work, but will be discussed in another paper.

An excellent review of the literature up to 1895 is found in the monograph of Billings, Mitchell, and Bergey on "The Composition of Expired Air and its Effects upon Animal Life" (published by the Smithsonian Institution). We therefore give only a brief summary of the more important references:

In 1863 Hammond demonstrated the presence of organic matter in vitiated air by experiments upon mice and also by passing the air vitiated by respiration through potassium permanganate. He confined a mouse under a large jar in which the carbon dioxide was taken up by baryta water as fast as it was formed and the moisture absorbed with calcium chloride. Nevertheless the mouse died in forty minutes. The observation was repeated a number of times and death ensued invariably in less than one hour. Brown-Séquard and D'Arsonval condensed the moisture in the exhaled breath, and the liquid thus collected was injected into the veins of rabbits. Death usually took place in a few days; sometimes in a few weeks. They believed from this that they had discovered a volatile organic poison of the nature of an alkaloid similar to

Brieger's ptomains. These experiments were repeated with variable results, but in 1889 they reported ingenious experiments in which they obtained additional evidence in support of their former statements. Rabbits were confined in a series of jars connected with rubber tubing permitting a constant current of air to be passed. The animal in the last jar received the air from the lungs of the animals in the other jars. This animal died after an interval of some hours and the animal in the next jar died next. The first and second animals usually remained alive. When they placed absorption tubes containing concentrated sulphuric acid between the last two jars the animal in the last jar remained alive while the one in the jar just before was the first to die. This confirmed their belief in the existence of a volatile poison absorbed by the sulphuric acid. Haldane and Smith repeated the experiments of Brown-Séquard and D'Arsonval, using five bottled mice. They continued the exposure for fifty-three hours without ill effects to the mice. Beu in 1893 also repeated these experiments and came to the conclusion that acute poisoning through the organic matters contained in the expired air was not possible and that the death of the animals was due to changes of temperature and accumulation of moisture in the jars. Rauer in 1893, also Lübberd and Peters, concluded from similar experiments that there are no organic poisons in the expired air.

Lehmann and Jessen in 1890 collected from 15 to 20 c.c. of condensed fluid per hour from the breath of a person exhaling through a glass spiral laid in ice. This fluid was always clear, odorless, neutral in reaction, and contained slight traces of ammonia from persons with good teeth; more from those with poor teeth. Inoculation of this condensed fluid into animals gave negative results. In 1894 Brown-Séquard and Davis reported further experiments in which they inoculated over one hundred animals with the condensed fluid of respiration, and not only confirmed their former statements but were unable to understand the failure of other experimenters, and emphatically reaffirmed that the breath contains a volatile poison and that the death of animals under experimental conditions is not due to an excess of carbon dioxide nor a deficiency of oxygen. This question was studied by Billings,

Mitchell, and Bergey in 1895, who came to the conclusion that the ill effects of a vitiated atmosphere depend almost entirely upon increased temperature and moisture and not to an excess of carbon dioxide or bacteria or dust of any kind.

It will be seen from this brief review that this question of the presence of organic matter in the expired breath is in confusion.

The present experiments were taken up in order to demonstrate, if possible, the presence of organic matter in the expired breath by means of the reaction of anaphylaxis. It is now generally recognized that the reaction of anaphylaxis is exceedingly delicate, for by its means we are enabled to distinguish so small a quantity as $\frac{1}{1000000}$ c.c. of blood serum or $\frac{1}{200000000}$ gram of purified egg-white—amounts far too small to detect by any chemical method. The reaction of anaphylaxis has the further advantage of being specific, so that if organic matters are found through this reaction their nature may be predicated.

The method adopted consisted, briefly, in condensing the vapors from the expired breath of man, injecting the liquid so obtained into guinea-pigs and, after an interval of several weeks or more, testing the guinea-pigs to determine whether they have become "hypersusceptible" to normal human blood.

The fact that the guinea-pigs showed a definite response clearly indicates that they were sensitized with a protein substance of human origin. This statement is based upon the fact now well established that guinea-pigs may be sensitized only with albuminous matter higher in structure than peptones, and the specific nature of the phenomenon makes it reasonably certain that the protein matter in this case must have been of human origin. At first sight it seems almost incredible to believe that such a complex molecule as protein may be volatile. Nevertheless, such appears to be the natural conclusion to draw from the results of our experiments. After all, the question of volatility may have much similarity to the question of solubility. Theoretically, all substances are soluble, although some in minute amounts; in the same sense all substances may be volatile. Volatility does not mean necessarily a change to the gaseous state in the sense that simple substances are volatile. Thus we may assume that solid and liquid substances may pass into the air in a state of "colloidal suspension." The simplest

conception would be to regard the protein as passing off in solution in the watery vapor. Whatever the physicochemical conception the inference is forced upon us that protein may pass into the air in the expired breath and be again collected in sufficient amounts to produce a definite biological reaction in susceptible animals.

The fact that organic substances, specific in nature, have been definitely demonstrated in the expired breath does not prove that these substances are poisonous. The physiological effect of such organic matter must now be studied.

The following tables show the work in some of its details. The negative as well as the positive results are reported. Only those series are omitted in which the experiments were spoiled by some accident.

ERIES II.—(*Some of the series have been omitted on account of the death of the animals or on account of some accident e experiments. All the negative results are included.*)

ctober 29, 1909.—Liquid condensed from the expired air of Amoss. Collected in accordance with method A. e of collection, eleven hours. Amount of liquid obtained, 15 c.c. Cultures of the liquid developed a spore-bearing nism of the subtilic group. The condensed liquid was warmed to 37° C. immediately after it was obtained and cted at once into the following guinea-pigs:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
12-4-09	5 c.c. liquid condensed from exp'd breath of Amoss	Subcutaneous	36 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Cough once in 5 minutes. Irregular respirations. Convulsions and general paralysis. (Chloroformed 3 hours after injection.)	Reaction masked by pressure symptoms. Autopsy showed basal hemorrhage.
12-4-09	5 c.c. same	Subcutaneous	36 days	0.5 c.c. same	Heart	Agitation in 1 minute. Cough, respirations irregular, jerky, wheezing, with expiration. Fur ruffled, shivering, wobbly, and down. (Chloroformed.)	Autopsy showed no mechanical cause of symptoms.
12-4-09	3 c.c. same	Subcutaneous	36 days	0.5 c.c. same	Heart	Coughing and scratching in less than 1 minute. Respiration labored, irregular, and jerky. Down.	Recovered.

Summary of Series II: Numbers 2 and 3 of this series showed a definite reaction.

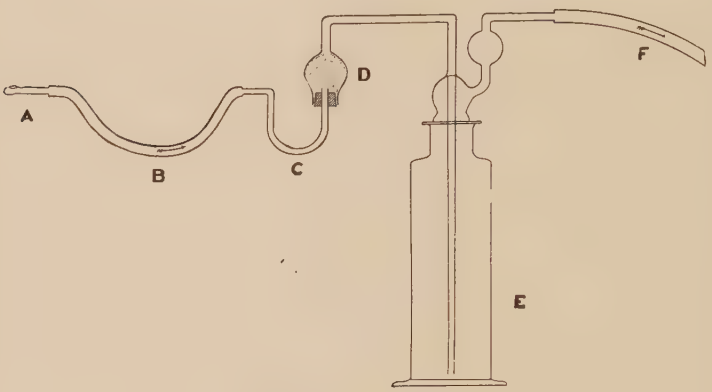

FIG. 1.—METHOD A. *A*, mouth-piece; *B*, rubber connection; *C*, trap; *D*, filter of glass wool; *E*, Drexel bottle which stands in an ice- and salt-freezing mixture; *F*, rubber connection to vacuum pump.

SERIES III.—November 1, 1909. Liquid condensed from the expired air of Amoss, six hours, then Kenney, three hours, into same Drexel bottle. Collected in accordance with method A. Time of collection, nine hours. Amount of liquid obtained, 17 c.c. Cultures from the liquid remained sterile. Remarks: Amoss had rhinitis with coryza. The liquid thus obtained was warmed to 31° C. for ten minutes and injected at once subcutaneously into the following guinea-pigs:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	12-4-09	8 c.c. liquid condensed from exp'd breath of Amoss and Kenney	Subcutaneous	33 days	0.5 c.c. normal human serum (Amoss)	Heart	No symptoms	
2	12-4-09	3 c.c. same	Subcutaneous	33 days	0.5 c.c. same	Heart	Ruffl'g and scratching	Symptoms suggestive but not positive.
3	12-4-09	5 c.c. same	Subcutaneous	33 days	0.5 c.c. same	Heart	No symptoms	

Local reactions: Series III, No. 1, Fluid slowly absorbed, slight edema and inflammation at site of injection. No. 2, no edema; slight induration at site of injection. No. 3, no edema; slight induration at sight of injection.

Summary of Series III: Only one of the three guinea-pigs in this series gave a suggestive reaction, but not regarded as positive in our conclusions.

IES IV.—November 4, 1909. Liquid condensed from the expired air of Amoss, eight hours, then Kenney, two into the same bottle. Collected in accordance with method A. Modified so as to reduce the chance of external nination, viz., several layers of sterile gauze being wrapped around the neck of the bottle. Time of collection, ours. Amount of liquid obtained, 24 c.c. Agar slants of one drop of this liquid showed growth in one tube; another rly inoculated remained sterile. The condensed liquid was frozen as soon as it was deposited and kept frozen g the entire time of collection, then the contents of the Drexel bottle were allowed to melt at room temper- and then warmed for six minutes in a water bath at 30° C. The liquid thus obtained was divided into parts, viz.: (*a*) Without further treatment injected at once into guinea-pigs. (*b*) Allowed to stand over at 5° C., then injected into guinea-pigs. (*c*) A small amount of alkali added and then allowed to stand night at 5° C., and then injected into guinea-pigs. (*d*) A small amount of acid added and then allowed to over night at 5° C., and then injected into guinea-pigs.

IES IV, A.—The following five guinea-pigs were sensitized with the liquid obtained at once after thawing and without further treatment:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
2-7-09	5 c.c. liquid condensed from exp'd breath of Amoss and Kenney	Subcutaneous	33 days	0.5 c.c. normal human serum (Amoss)	Heart	Expiratory difficulty, scratching, coughed in 4 minutes, drowsy, fur ruffled, shivering. Symptoms subsided in 30 minutes. (Chloroformed.)	Autopsy: no mechanical cause of symptoms found.
2-7-09	4 c.c. same	Subcutaneous	33 days	0.4 c.c. same	Heart	Shivering, breathing expulsive, coughing motions (no sound). Quiet in ½ hour. (Chloroformed.)	Autopsy: no mechanical cause of symptoms.
2-7-09	3 c.c. same	Subcuta-	33 days	0.1 c.c. same	Heart	Agitation and shivering, scratching. Symptoms subsided. (Chloroformed.)	Autopsy: clot in pericardium.
2-7-10	2 c.c. same	Subcutaneous	33 days	0.1 c.c. same	Heart	Typical reaction: scratchi'g, coughed in 6 minutes, down, fur ruffled, etc. (Chloroformed.)	Autopsy: Small clot around base of heart.
2-7-10	1 c.c. same	Subcutaneous	33 days	0.2 c.c. same	Heart	No symptoms	Autopsy revealed very small clot in pericardium.

SERIES IV, B.—2.6 c.c. of the liquid was made up to 3 c.c. with sterile water and allowed to stand for fourteen one-half hours at 5° C., when it was warmed to 20° C. for five minutes and then injected into the following guinea-p (the liquid was diluted in this experiment to serve as a control for Series IV, C and IV, D.):

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
6	12-7-09	3 c.c. liquid condensed from exp'd breath of Amoss and Kenney and allowed to stand at 5° C. for 14° hours	Subcutaneous	32 days	0.1 c.c. normal human serum (Amoss)	Heart	Coughing, scratching, expiratory difficulty, agitation, typical convulsions, hiccough. Typical reaction. Recovered. (Chloroformed.)	Autopsy: no mechanical ca of symptoms

SERIES IV, C.—2.6 c.c. of the liquid was placed in a sterile test-tube, with 0.3 c.c. of normal sterile sodium bicarbon solution, and 0.1 c.c. of sterile water (this makes a solution of 3 c.c. of $\frac{N}{10}$ sodium bicarbonate). The test-tube allowed to stand over night (fourteen and one-half hours) at 5° C., then warmed at 20° C. for five minutes and injec subcutaneously into guinea-pig No. 7.

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
7	12-7-09	3 c.c. liquid allowed to stand in alkaline solution	Subcutaneous	32 days	0.1 c.c. normal human serum (Amoss)	Hear	.....	Died of peri dial hemorrha

SERIES IV, D.—2.6 c.c. of the liquid was placed in a sterile test-tube with 0.3 c.c. of $\frac{N}{100}$ sterile hydrochloric a and 0.1 c.c. sterile water added (this makes a solution of 3 c.c. $\frac{N}{1000}$ HCl). The tube was allowed to stand fourteen and one-half hours at 5° C., when it was warmed at 20° C. for five minutes and then injected subcutaneou into guinea-pig No. 8.

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
8	12-7-09	3 c.c. liquid allowed to stand in acid solution	Subcutaneous	32 days	0.1 c.c. normal human serum (Amoss)	Heart	Coughing, convulsive expiration, agitation, scratching. Typical reaction. Recovered. (Chloroformed.)	Autopsy: no chanical ca of symptom

Summary of Series IV: The experiments in Series IV were evidently designed to test the effect of time, and action of acids and alkalies on the organic matter in the condensed liquid from the expired breath. The results s that guinea-pigs may be sensitized even though the liquid is kept for fourteen and one-half hours, cold, and in dark; and further, that a minute amount of acid had no effect so far as may be judged from the limited data. effect of the presence of the alkali was not determined on account of the accident to the animal.

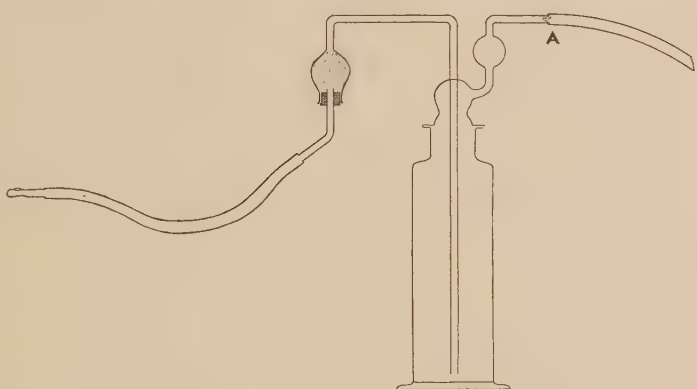

FIG. 2.—METHOD B. Similar in all respects to method A, excepting the form of the trap, and an additional cotton filter at *A*, to prevent contamination from the outlet of the Drexel bottle. As a further guard against contamination, the neck of the Drexel bottle in this and all subsequent methods was swathed with several layers of sterile gauze.

ERIES V.—December 17, 1909. Liquid condensed from the expired air of Amoss. The material was collected in ordance with method B. Time of collection, seven and one-half hours. Amount of liquid obtained, 50 c.c. The densed liquid was kept frozen in this experiment except for a short interval when it thawed, but was again frozen. e liquid was kept in the Drexel bottle for fifteen hours at 5° C., then warmed and injected into guinea-pigs as indi- ed in the following table. Cultures showed the liquid to be sterile. Biuret and Millon's tests were negative. The ss wool in this experiment was not discolored, as it was in many of the experiments. All tubing and connections :e of larger bore than those used in previous experiments, thereby allowing more expired air to pass through in a en time.

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
4-1-10	5 c.c. liquid condensed from exp'd air of Amoss	Subcutaneous	103 days	0.1 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Negative.	
4-1-10	4 c.c. same	Subcutaneous	103 days	0.1 c.c. same	Brain (through optic foramen)	Negative.	
4-1-10	3 c.c. same	Subcutaneous	103 days	0.1 c.c. same	Brain (through optic foramen)	Convulsive movements. Down, sneezed, coughed.	
4-1-10	2 c.c. same	Subcutaneous	103 days	0.1 c.c. same	Brain (through optic foramen)	Negative.	
4-1-10	1 c.c. same	Subcutaneous	103 days	0.1 c.c. same	Brain (through optic foramen)	Symptoms masked (?).	
4-1-10	4 c.c. same	Subcutaneous	103 days	0.2 c.c. same	Brain (through optic foramen)	Symptoms masked (?).	
4-1-10	3 c.c. same	Subcutaneous	103 days	0.2 c.c. same	Brain (through optic foramen)	Symptoms masked (?).	
4-1-10	2 c.c. same	Subcutaneous	103 days	0.2 c.c. same	Brain (through optic foramen)	Symptoms masked (?).	
4-1-10	2 c.c. same (heated)[1]	Subcutaneous	103 days	0.5 c.c. same	Brain (through optic foramen)	Symptoms masked (?).	

Summary of Series V: Only one of the animals in this series showed suggestive symptoms; all the remainder were sidered negative.

The liquid in the case of guinea-pig No. 12 was heated for half an hour in the covered sterilizer before it was ected.

SERIES VI.—December 17, 1909. Liquid condensed from the expired air of Kenney. Collected in accordan with method B. Time of collection, six and one-half hours with one and one-half hour interval after the first four hou Amount of liquid obtained, 18 c.c. The warmed glass wool used to filter the expired air was not discolored. Cultu of the liquid were sterile. The liquid was allowed to remain in the Drexel bottle at 5° C. for fifteen hours, then warm to about 30° C. and injected into guinea-pigs subcutaneously as indicated in the following table:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	5-14-10	5 c.c. liquid condensed from exp'd breath of Kenney	Subcutaneous	147 days	0.1 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Symptoms masked.	
2	5-14-10	4 c.c. same	Subcutaneous	147 days	0.2 c.c. same	Brain (through optic foramen)	Restless in 15 minutes	Reaction mask
4	5-14-10	3 c.c. same	Subcutaneous	147 days	0.5 c.c. same	Brain (through optic foramen)	Symptoms of pressure.	
5	5-14-10	2 c.c. same	Subcutaneous	147 days	0.5 c.c. same	Brain (through optic foramen)	Symptoms masked.	
6	5-14-10	1 c.c. same	Subcutaneous	147 days	0.3 c.c. same	Brain (through optic foramen)	Symptoms masked.	

Summary of Series VI: The results of this series were regarded as negative.

SERIES VII.—December 17, 1909. Liquid condensed from the expired air of Miss J. Collected in accordance w method B except the Drexel bottle was smaller (16 ounces instead of 32). Time of collection, six and one-half hou Amount of liquid obtained, 40 c.c. The liquid was frozen after the second hour of collection. Culture media inocula with the liquid remained sterile. The glass wool used as a filter for the expired air was not discolored. The fro condensed liquid was allowed to remain at a temperature of 5° C. for eighteen hours, then warmed to about 30° in a water-bath and injected subcutaneously into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
2	5-14-10	4 c.c. liquid condensed from exp'd breath of Miss Jones	Subcutaneous	147 days	0.2 c.c. normal human serum (Amoss)	Brain (through right optic foramen)	Symptoms masked.	
9	5-14-10	2 c.c. same	Subcutaneous	147 days	0.2 c.c. same	Brain (through right optic foramen)	Symptoms masked.	

Summary of Series VII: The results of this series were regarded as negative.

Control. At this point in the work a control was made of the instruments, apparatus, and methods used. This was done to eliminate any faults in the technique by which traces of human protein might have been overlooked. It is well known that it requires exceedingly small amounts of protein to sensitize a guinea-pig.

ecember 18, 1909. Using same kind of pipettes, syringes, apparatus, etc., with conditions as nearly alike as possible nose of Series V, VI, and VII, salt solution was injected instead of liquid condensed from the expired air as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
5-14-10	5 c.c. salt solution	Subcutaneous	72 days	0.2 c.c. normal human serum (Amoss)	Brain (through right optic foramen)	Brain injury. Killed by chloroform.	
5-14-10	5 c.c. same	Subcutaneous	72 days	0.2 c.c. same	Brain (through right optic foramen)	Negative.	

ERIES VIII.—May 26, 1910. Liquid condensed from expired air of Amoss. Collected in accordance with method Liquid did not freeze. Time of collection, six hours. Total amount collected, 26 c.c. The liquid was allowed to nd for twenty-five minutes at room temperature and while still cold was injected into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
6-2-10	10 c.c. liquid condensed from exp'd breath of Amoss	Subcutaneous	26 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	No reaction.	
6-2-10	6 c.c. same	Subcutaneous	26 days	0.2 c.c. same	Brain (through optic foramen)	No reaction.	
6-2-10	5 c.c. same	Subcutaneous	26 days	0.2 c.c. same	Brain (through optic foramen)	No reaction.	

SERIES IX.—May 26, 1910. Liquid condensed from the expired air of Miss J. Collected in accordance with method Time of collection, five hours. Amount of condensed liquid, 40 c.c. Liquid did not freeze. Considerable foam in e condensed liquid during collection; this foaming started at about the beginning of the second hour when the ndensed liquid reached the height of the inlet tube. The liquid was allowed to stand at room temperature for enty-five minutes and injected into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
6-21-10	10 c.c. liquid condensed from exp'd breath of Miss Jones	Subcutaneous	26 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Scratched vigorously; coughed, agitation, dyspnea, down, cyanotic	Typical reaction.
6-21-10	10 c.c. same	Subcutaneous	26 days	0.2 c.c. same	Brain (through optic foramen)	Expulsive coughing, scratching, down in 8 minutes	Positive.
6-21-10	10 c.c. same	Subcutaneous	26 days	0.2 c.c. same	Brain (through optic foramen)	Agitation and down	Positive.

Guinea-pig No. 1 in this series had a small slough at the site of the first injection, and guinea-pigs Nos. 2 and 3 h had a large slough.

Summary of Series IX: All three guinea-pigs in this series reacted.

SERIES X.—May 27, 1910. Liquid condensed from the expired air of Amoss. Collected in accordance with met
B. Time of collection, five hours. Amount of liquid condensed, 50 c.c. Air began to bubble through the liquid, wh
condensed by the beginning of the third hour. Injected at once after collection.

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	6-21-10	10 c.c. liquid condensed from exp'd breath of Amoss	Subcutaneous	25 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Wheezing, expulsive and jerky respiration, down	Suggestive sym toms masked central irritat
2	6-21-10	10 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	Agitation	?
3	6-21-10	10 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	Agitation	?
4	6-21-10	10 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	No reaction	
5	6-21-10	7 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	Down in 4 minutes	?

Guinea-pigs Nos. 1 and 2 had no slough at site of first injection. Guinea-pigs Nos. 3, 4, and 5 had a slough at s
of first injection.

Summary of Series X: Whether the reactions in this series were those of anaphylaxis or not may be conside
doubtful.

SERIES XI.—May 27, 1910. Liquid condensed from the expired air of Miss J. Collected in accordance with meth
B, using a 16-ounce Drexel bottle. Time of collection, five hours. Amount of liquid obtained, 33 c.c. Injected
once after the liquid was obtained.

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	6-21-10	10 c.c. liquid condensed from exp'd breath of Miss Jones	Subcutaneous	25 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Great agitation, down in 14 minutes, convulsions	Positive.
2	6-21-10	10 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	Cough, agitation, down in 13 minutes	Positive.
3	6-21-10	10 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	Cough, down in 10 minutes	Positive.
4	6-21-10	3 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	Agitation, cough, scratching, down in 9 minutes	Positive.

Summary of Series X: All four of the animals in this series developed slough at the site of the first injection.
four gave a definite reaction of anaphylaxis.

ERIES XII.—May 27, 1910. Liquid condensed from the expired air of Kenney. Collected in accordance with hod B. Time of collection, five and one-half hours. Amount of liquid obtained, 16 c.c. The liquid thus condensed injected at once into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
6-21-10	10 c.c. liquid from exp'd breath of Kenney	Subcutaneous	25 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Negative	Chloroformed.
6-21-10	6 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	?	Chloroformed.

ERIES XIII.—May 28, 1910. Liquid condensed from the expired air of Amoss. Collected in accordance with hod B. Time of collection, three hours. Amount of liquid collected, 30 c.c. Injected immediately (after having warmed) into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
6-21-10	10 c.c. liquid from condensed expired breat of Amoss	Subcutaneous	25 days	0.2 c.c. normal human serum (Morse)	Brain (through optic foramen)	Agitation down and up, jerky respiration	Positive.
6-21-10	10 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	No reaction	Negative.
6-21-10	10 c.c. same	Subcutaneous	25 days	0.2 c.c. same	Brain (through optic foramen)	Down, jerky respiration, agitation, cough	Positive.

ummary of Series VIII: Guinea-pig No. 1 had no slough; Nos. 2 and 3 developed slough at site of first injection. o of the three animals of this series gave a definite reaction of anaphylaxis.

SERIES XIV.—May 28, 1910. Liquid condensed from the expired air of Miss J. Collected in accordance w method B, using 16-ounce Drexel bottle. Time of collection, three and one-half hours. Amount of collection, 26 Warmed and injected at once into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	6-21-10	10 c.c. liquid condensed from exp'd breath of Miss Jones	Subcutaneous	24 days	0.2 c.c. normal human serum (Morse)	Brain (through optic foramen)	?	
2	6-21-10	10 c.c. same	Subcutaneous	24 days	0.2 c.c. same	Brain (through optic foramen)	Respiratory difficulty, down, convulsions, paralysis. Died in 4 hours	Positive
3	6-21-10	6 c.c. same	Subcutaneous	24 days	0.2 c.c. same	Brain (through optic foramen)	Cough, respiratory difficulty, convulsions, paralysis. Died in 3 hours	Positive.

Summary of Series XIV: Guinea-pigs Nos. 2 and 3 each developed a slough at site of first injection. Guinea- No. 1 did not develop a slough at site of first injection. Two of these three animals developed definite symptom anaphylaxis.

SERIES XV.—June 1, 1910. Liquid condensed from the expired air of Kenney. Collected in accordance w method B. Time of collection, five and one-half hours with a one-hour interval after the third hour. Amount liquid obtained, 48½ c.c. Liquid thus collected was brought to room temperature and injected immediately i the following guinea-pigs:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	6-21-10	10 c.c. liquid condensed from exp'd breath of Kenney	Subcutaneous	20 days	0.2 c.c. normal human serum (Morse)	Brain (through optic foramen)	Jerky respirations and apparently ill	Recovered.
2	6-21-10	0.9 c.c. same	Subcutaneous	20 days	0.2 c.c. same	Brain (through optic foramen)	Injury at base of brain	Chloroformed
3	6-21-10	0.9 c.c. same	Subcutaneous	20 days	0.2 c.c. same	Brain (through optic foramen)	Jerky respirations and apparently ill	Recovered.
4	6-21-10	0.9 c.c. same	Subcuta-	20 days	0.2 c.c. same	Brain (through optic foramen).	?	
5	6-21-10	0.9 c.c. same	Subcutaneous (Probably some intraperitoneally)	20 days	0.2 c.c. same	Brain (through optic foramen)	Agitation, cough, scratching, down.	
6	6-21-10	2.5 c.c. same	Subcutaneous	20 days	0.2 c.c. same	Brain (through optic foramen)	Agitation, scratching, convulsions running movements, down	Recovered.

Summary of Series XV: No. 4 in this series was the only guinea-pig that developed a slough at site of the fi injection. Four of the six guinea-pigs in this series showed definite indications of anaphylaxis.

ERIES XVI.—July 12, 1910. Liquid condensed from the expired air of Amoss. Collected in accordance with hod C. Time of collection, six hours. Total amount collected, 46 c.c. The liquid was warmed to about 20° C. injected immediately into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
8-13-19	10 c.c. liquid condensed from exp'd breath of Amoss	Subcutaneous	32 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Restless, washed face, fur ruffled, scratching.	
8-13-10	10 c.c. same	Subcutaneous	32 days	0.2 c.c. same	Brain (through optic foramen)	Appeared uncomfortable, furruffled, shivering.	
8-13-10	10 c.c. same	Subcutaneous	32 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms.	
8-13-10	10 c.c. same	Subcutaneous	32 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms.	
8-13-10	6 c.c. same	Subcutaneous	32 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms.	

ummary of Series XVI: Guinea-pig No. 3 developed small slough at site of first injection, the others none at all. this series only the first two animals developed mild symptoms that may have been indications of anaphylaxis.

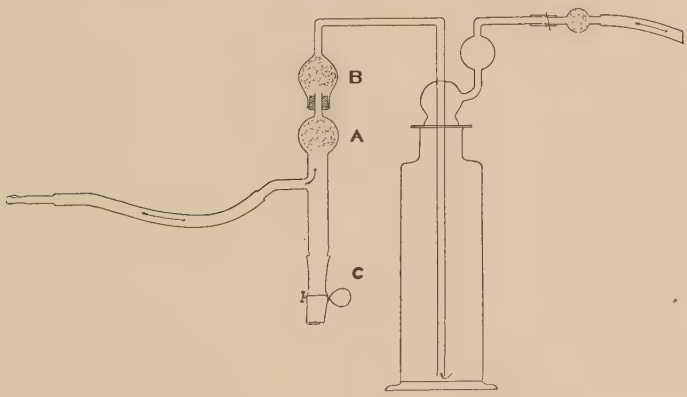

FIG. 3.—METHOD C. The apparatus in this method contained two glass-wool filters, *A* and *B*, and an improved trap controlled with a Mohr's pinchcock. The bulbs *A* and *B* were surrounded with a box warmed with a 16-candle power electric globe and the temperature controlled by a thermometer between 37° and 40° C.

SERIES XVII.—July 13, 1910. Liquid condensed from the expired air of Amoss. Collected in accordance method C. Time of collection, seven and one-half hours; one-hour interval after the fourth hour. Amount colle 51 c.c. The liquid was warmed and injected immediately into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks
2	8-13-10	10 c.c. liquid condensed from exp'd breath of Amoss	Subcutaneous	31 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Negative.	
3	8-13-10	10 c.c. same	Subcutaneous	31 days	0.2 c.c. same	Brain (through optic foramen)	Negative.	
4	8-13-10	10 c.c. same	Subcutaneous	31 days	0.2 c.c. same	Brain (through optic foramen)	Negative	Slight slough site of first jection.
5	8-13-10	9 c.c. same	Subcutaneous	31 days	0.2 c.c. same	Brain (through optic foramen)	Negative.	
6	8-13-10	2 c.c. same	Subcutaneous	31 days	0.2 c.c. same	Brain (through optic foramen)	Negative.	

SERIES XVIII.—July 14, 1910. Liquid condensed from the expired air of Amoss. Collected in accordance method C. Time of collection, six hours. Amount of liquid obtained, 34 c.c. The liquid was allowed to stan room temperature for two hours and injected into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks
1	8-13-10	10 c.c. liquid condensed from exp'd breath of Amcss	Subcutaneous	30 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	No symptoms	Negative.
2	8-13-10	10 c.c. same	Subcutaneous	30 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms	Negative.
3	8-13-10	10 c.c. same	Subcutaneous	30 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms	Negative.
4	8-13-10	4 c.c. same	Subcutaneous	30 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms	Negative.

Number 2 of this series had a considerable slough at site of first injection.

IES XXI.—July 20, 1910. Liquid condensed from the expired air of Amoss and Kenney into same apparatus. ted in accordance with method C. Time of collection, four hours Amoss, and one hour Kenney. Amount of obtained, 40 c.c. Liquid was warmed to about 30° C. and at once injected into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
8-13-10	10 c.c. liquid condensed from exp'd breath of Amoss	Subcutaneous	24 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	No symptoms.	
8-13-10	10 c.c. same	Subcutaneous	24 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms.	
8-13-10	10 c.c. same	Subcutaneous	24 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms.	

No sloughs following first injection in this series.

IES XXII.—July 22, 1910. Liquid condensed from the expired air of Amoss. Collected in accordance with od C. Time of collection, five hours. Amount of liquid obtained, 40 c.c. The liquid was allowed to come to a erature of 30° C. and at once injected into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
8-13-10	10 c.c. liquid condensed from exp'd breath of Amoss	Subcutaneous	22 days	0.2 c.c. normal human serum (Amoss)	Brain (through optic foramen)	No symptoms	No slough.
8-13-10	10 c.c. same	Subcutaneous	22 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms	Some slough.
8-13-10	10 c.c. same	Subcutaneous	22 days	0.2 c.c. same	Brain (through optic foramen)	No symptoms	No slough.
8-13-10	10 c.c. same	Subcutaneous	22 days	0.2 c.c. same	Brain (through optic foramen)	Convulsive movements; jerky respirations	No slough.

SERIES XXXIV.—May 19, 1911. Liquid condensed from expired breath of K., Miss P., S., A., Miss D. and R., one using separate apparatus; collected in accordance with method C. Time of collection: K., one hour; Mi four hours; S., two hours; A., one hour; Miss D., three hours; R., two hours. Amount of liquid obtained: K., Miss P., 30 c.c.; S., 23 c.c.; A., 11 c.c.; Miss D., 34 c.c.; R., 20 c.c. K. used a 32-ounce Drexel bottle; liquid was frozen; the glass wool not discolored; liquid clear; no bubbling. Miss P. used a 32-ounce Drexel bottle; liquid frozen; had yellow tinge; the glass wool was not discolored; there was foaming S. used a 64-ounce Drexel b liquid half frozen; opalescent and foamed; glass wool was not discolored and there was a large amount of saliva i trap. A. used a 32-ounce Drexel bottle; liquid was very slightly frozen; clear; no color; no foaming; glass woo discolored. Miss D. used a 64-ounce Drexel bottle; liquid was never frozen; clear; no saliva; glass wool was no colored. R. used a 16-ounce Drexel bottle; liquid was frozen; clear; there was bubbling after the second hour an glass wool was slightly discolored (tobacco ?). One-half cubic centimeter of the liquid from each was inoculated plain broth; there was no growth except in the case of S. (staining showed the flora to be of salivary origin). various amounts of liquid were immediately warmed to 35° C. and injected at once into the following guinea-pi

No.	Date of second injection	First injection.	Site.	Interval	Second injection.	Site.	Result.	Remark
1	6-15-11	9 c.c. liquid condensed from exp'd breath of Kenney	5 c.c. into peritoneum; 4 c.c. subcutaneously	27 days	0.2 c.c. normal human serum (Amoss)	Heart	Fur ruffled	Negative.
3	6-15-11	10 c.c. liquid condensed from exp'd breath of P.	Subcutaneous	27 days	0.2 c.c. same	Heart	Shivering	Negative.
4	6-15-11	10 c.c. same	Peritoneum	27 days	0.2 c.c. same	Heart	Shivering; sudden expiratory movements	Negative.
5	6-16-11	10 c.c. liquid condensed from exp'd air of S.	Peritoneum	28 days	0.5 c.c. same	Heart	Washed face; agitative; down; looks sick. (Chloroformed.)	Autopsy: in pericar Spurted opened.
6	6-16-11	10 c.c. same	Subcutaneous	28 days	0.5 c.c. same	Heart	Negative	
7	6-16-11	3 c.c. same	Peritoneum	27 days	0.5 c.c. same	Heart	Negative	
8	6-15-11	11 c.c. liquid condensed from exp'd breath of A.	Subcutaneous	27 days	0.35 c.c. same	Heart	Shivering	Negative.
9	6-15-11	10 c.c. liquid condensed from exp'd breath of D.	Subcutaneous	27 days	0.4 c.c. same	Heart	Negative	
10	6-15-11	10 c.c. same	Peritoneum	27 days	0.4 c.c. same	Heart	Cough in 1 minute; agitation; jerky respirations; cyanotic. Down in 4 minutes and up. Limp. Recovered. (Chloroformed.)	Autopsy: I chanical of symp Lungs Pericar O.K.

SERIES XXXIV.—*Continued.*

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
6-15-11	10 c.c. same	Subcutaneous	27 days	0.4 c.c. same	Heart	Cough in 1 minute; respiratory difficulty; down. Convulsions. Died in 4 minutes	Autopsy: No mechanical cause of symptoms. No lesions in pericardium. Heart continued to beat after cessation of respirations. Lungs full when removed do not collapse.
6-15-11	4 c.c. same	Subcutaneous	27 days	0.4 c.c. same	Heart	Cough in ½ minute; agitation; cyanosis; respiratory difficulty. Convulsions in 2 minutes. Died in 4 minutes. Heart continued to beat after respirations stopped	Autopsy: Slight amount of blood in pericardium. Heart beat at least 10 minutes after being exposed.
6-16-11	10 c.c. liquid condensed from exp'd breath of R.	Peritoneum	28 days	0.5 c.c. same	Heart	Scratching; agitation; respiratory difficulty; cough in 2 minutes. Down in 5 minutes. Looks sick; irregular respirations. Typical symptoms (Chloroformed.)	Autopsy: Pericardium O.K No mechanical cause of symptoms.
6-16-11	10 c.c. same	Subcutaneous	28 days	0.5 c.c. same	Heart	Negative.	

Summary of Series XXIV: Of the animals in this series 4 responded typically; 2 died.

ERIES XXXV.—May 27, 1911. Liquid condensed from the expired breath of A. Collected in accordance with hod C. Time of collection, five hours. Amount of collection, 35 c.c. Liquid frozen during entire experiment. oaming or bubbling. The glass wool was not discolored. One-half c.c. of the liquid inoculated into broth showed rowth. The liquid was warmed to 35° C. and injected immediately into a guinea-pig.

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
6-16-11	35 c.c. liquid condensed from exp'd breath of A.	Subcutaneous	20 days	0.5 c.c. normal human serum (Amoss)	Heart	Negative.	

Saliva Control. One possible source of error was kept in mind throughout these experiments, that is, that particles of saliva might pass the barrier of the cotton wool and appear in the condensed liquid. If guinea-pigs can be sensitized with saliva the least fault in technique in this regard would render the results misleading. Every precaution was taken to prevent this accident. The bulbs were tightly stuffed with glass wool and the fact that bacteria did not get through is a fair indication that other particulate matter did not pass.

It becomes important to know whether guinea-pigs sensitized with saliva will respond after a proper interval to a second injection of human blood serum.

In the following experiments, Series XXIX, XXX, and XXXI, the guinea-pigs were given a first injection of an amount of saliva far in excess of any quantity that could possibly have been contained in the liquid condensed from the expired breath under the conditions of our experiments. At the second injection they were given normal human serum in the same amounts and by precisely the same methods used to demonstrate the presence of organic matter in the expired breath.

The guinea-pigs injected with human saliva gave practically no response to a second injection of human blood serum.

SERIES XXIX.—*Saliva.* November 30, 1910. The mouth was thoroughly cleansed with boric acid solution, th with sterile salt solution and a few cubic centimeters of saliva were collected into a sterile test glass. The saliva w diluted with sterile salt solution in the ratio of 1 to 10, when it was divided into three portions: (1) Without furth treatment; (2) passed through a Berkefeld filter, and (3) chloroformed. The first portion (without further treatmer was injected immediately into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	12-29-10	1 c.c. (representing 0.1 c.c. saliva)	Subcutaneous	43 days	0.1 c.c. normal human serum (Amoss)	Brain (through optic foramen)	No symptoms.	
3	12-29-10	1 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	No symptoms.	
7	12-29-10	1 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	No symptoms.	

Guinea-pigs Nos. 2, 4, 5, and 6 died from infection.

SERIES XXX.—*Filtered Saliva.* November 30, 1910. The second portion of the saliva described in Series XXIX s passed through a Berkefeld filter and injected into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1-12-11	5 c.c. filtered saliva (representing 0.5 c.c. saliva)	Subcutaneous	43 days	0.1 c.c. normal human serum (Amoss)	Brain (through optic foramen)	Wheeze, scratched head	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Down and up immediately	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Restless, agitation.	
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	No symptoms	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Respirations rapid	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Back up, fur ruffled	Negative.
1-12-11	1 c.c. filtered saliva (representing 0.1 c.c. saliva)	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Jerky movements	Negative.

SERIES XXXI.—*Saliva Chloroformed.* November 30, 1910. The third portion of the saliva was allowed to stand contact with chloroform, 1 c.c. of chloroform to 50 c.c. of diluted saliva, for twenty hours, at which time the chloroform was evaporated under reduced pressure and the saliva thus treated injected into guinea-pigs as follows:

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1-12-11	5 c.c. saliva treats with chloroform (representing 0.5 c.c. saliva)	Subcutaneous	43 days	0.1 c.c. normal human serum (Amoss)	Brain (through optic foramen)	No symptoms	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	No symptoms	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Injury to brain	Chloroformed.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Injury to brain	Chloroformed.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	No symptoms	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	Jerky respirations	Negative.
1-12-11	5 c.c. same	Subcutaneous	43 days	0.1 c.c. same	Brain (through optic foramen)	No symptoms	Negative.

SERIES XXIX, XXX, and XXXI. The following experiments were designed to determine whether albuminous substances such as eggs, milk, or blood could be "volatilized" sufficiently to demonstrate protein in the condensed fluid. Dry, filtered air was passed through the milk and over the eggs and blood, and then condensed in a Drexel bottle set in an ice and salt mixture. The liquid thus condensed was injected into guinea-pigs, and after a suitable interval the animals were tested to determine their hypersusceptibility.

SERIES XXIII.—*Eggs.* July 23, 1910. Liquid condensed from the air which had passed over whole eggs. was allowed to pass through concentrated sulphuric acid, then through a drying tower containing lime, thence t horizontal tube 3 inches in diameter and 3 feet long half filled with whole whipped eggs, where it was allowed to p over the surface, and was then drawn into the apparatus previously described as being used for collecting the liq from the expired air. Glass wool was put in the large tube with the eggs in order to assist in the evaporation, found to be worthless for this purpose. The tube was kept warm to 35° C. by coils of rubber tubing, through wh water at this temperature was run. The experiment began at 7.30 A.M. and ran until 6 P.M. About 36 c.c. of liq was condensed in the Drexel bottle. This was allowed to come to room temperature and injected at 7.30 P.M. i the following guinea-pigs:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
2	8-18-10	10 c.c. liquid condensed from eggs	Subcutaneous	26 days	9 c.c. saturated solution white of egg	Intraperitoneum	Negative.	
3	8-18-10	10 c.c. same	Subcutaneous	26 days	9 c.c. saturated solution white of egg	Intraperitoneum	Negative.	
4	8-18-10	10 c.c. same	Subcutaneous	26 days	9 c.c. saturated solution white of egg	Intraperitoneum	Jerky respirations. Looks sick; sprawling.	

The negative results with eggs may in part be accounted for by the fact that the egg mass in the horizontal t (see Fig. 5) soon became dry and hard upon the surface, thereby preventing further evaporation. It is not practi to bubble the air through the egg mixture as in the case of milk on account of foaming.

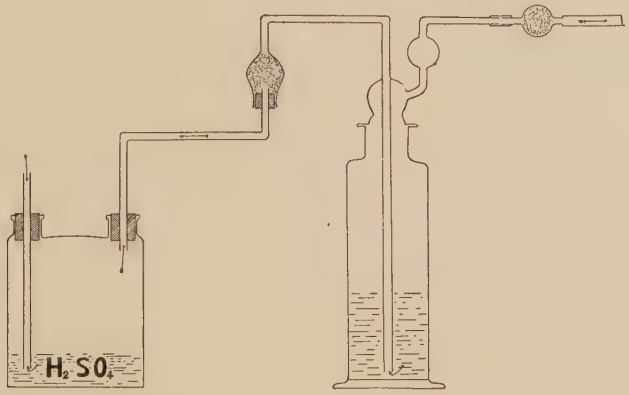

FIG. 4.—METHOD D. *Apparatus Used for the Experiments with Milk.* The air was first passed through a Woulfe's bottle containing concentrated sulphuric acid, then filtered through glass wool and bubbled through the milk in the first Drexel bottle and the vapors thus collected were condensed in a second Drexel bottle not shown in the diagram.

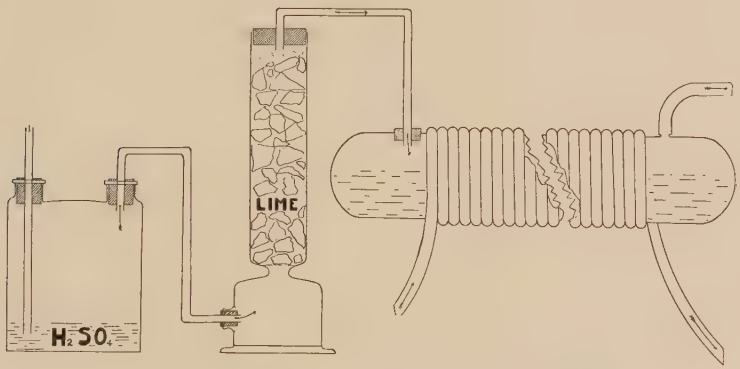

FIG. 5.—METHOD E. *Method Used in the Experiments with Egg and Blood.* The air was first dried, being passed through concentrated sulphuric acid in a Woulfe's bottle and then through a tower containing lime. The dried air was conducted over the surface of the eggs or the blood in a horizontal glass tube 3 inches in diameter and 3 feet long, thence to a Drexel bottle (not shown in the diagram) standing in a freezing mixture, where the moisture was condensed. The horizontal tube was surrounded with a coil of rubber tubing through which was circulating warm water at 37° C.

SERIES XXVI.—*Egg White.* July 28, 1910. Liquid condensed from the air which had been allowed to pass
the surface of the white of eggs. Collected in accordance with method E. The whites of eighteen fresh eggs were
into the horizontal tube. The air was allowed to pass over the surface of the whites of eggs from 7.30 A.M. until 3
Amount of liquid obtained was about 36 c.c. This was allowed to come to a temperature of about 30° C. and inje
immediately into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	8-18-10	10 c.c. condensations from air passed over whites of eggs	Subcutaneous	22 days	9 c.c. saturated solution white of egg	Intraperitoneum	No symptoms.	
2	8-18-10	10 c.c. same	Subcutaneous	22 days	9 c.c. same	Intraperitoneum	No symptoms.	
5	8-18-10	3 c.c. same	Subcutaneous	22 days	9 c.c. same	Intraperitoneum	No symptoms.	

SERIES XXIV.—*Milk.* July 26, 1910. Liquid condensed from the air which was passed through whole milk. C
lected in accordance with method D; 200 c.c. of fresh whole milk from the "Warelands" was used in the experim
which began at 10 A.M. July 26, and continued until 10 P.M., when the liquid condensed in the second Drexel bo
was warmed to 30° C. and injected into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	7-26-10	10 c.c. condensations from air bubbled through fresh milk	Subcutaneous	23 days	6 c.c. fresh milk	Intraperitoneum	No symptoms.	
3	7-26-10	10 c.c. same	Subcutaneous	23 days	6 c.c. fresh milk	Intraperitoneum	No symptoms.	
4	7-26-10	3 c.c. same	Subcutaneous	23 days	6 c.c. fresh milk	Intraperitoneum	No symptoms.	

ERIES XX.—*Milk.* July 18, 1910. Liquid condensed from the air which had passed through milk preserved with .c acid. At the same time that Series XIX was being run another similar series was carried out under conditions learly the same as possible except that the 200 c.c. of milk was preserved with 4 grams of boric acid. Amount of id collected, 30 c.c. Time of collection, seven hours. It was injected into 3 guinea-pigs as noted in the following le. The second injection consisted of 6 c.c. of fresh milk as in Series XIX.

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
8-13-10	10 c.c. condensation from milk preserved with H_3BO_4	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	No symptoms.	
8-13-10	10 c.c. same	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	Fur ruffled; looks sick; down.	
8-13-10	10 c.c. same	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	Fur ruffled; looks sick.	

The results are definite enough to suggest positive reactions.

ERIES XIX.—*Milk.* July 18, 1910. Whole fresh milk—200 c.c. (milked into sterile bottles at the "Warelands" M. July 18) was placed in sterile Drexel bottle at 7.40 A.M. The bottle was placed into a water bath maintained at C. Condensed liquid collected in accordance with method D (which see). Duration of experiment, seven and -half hours. Amount of liquid obtained was 70 c.c. The liquid was warmed at room temperature and injected guinea-pigs as follows (the second injection consisted of 6 c.c. of fresh milk from the same dairy taken under same conditions as the 200 c.c. used in the first part of the experiment):

Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	First injection.	Remarks.
8-13-10	10 c.c. condensation from milk	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	No symptoms.	
8-13-10	10 c.c. same	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	No symptoms.	
8-13-11	10 c.c. same	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	Fur ruffled; looks sick.	
8-13-10	10 c.c. same	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	Slight scratching; looks uncomfortable.	
8-13-10	10 c.c. same	Subcutaneous	25 days	6 c.c. fresh milk	Intraperitoneum	Fur ruffled; looks sick.	

While some of the animals in this series showed very slight symptoms, the reaction was not definite enough to be sidered as positive. It will be remembered that milk is not as toxic at the second injection for guinea-pigs as blood um or egg-white.

SERIES XXV.—*Blood.* July 27, 1910. Liquid condensed from the air which had been allowed to pass over surface of fresh defibrinated blood of a calf. Collected in accordance with method E (Fig. 5). The defibrinated blood was put into the horizontal tube and the dry air was allowed to pass over its surface from 3 P.M., July 26 8 A.M., July 27. Amount of liquid obtained was about 40 c.c. This was brought to a temperature of about 30° and injected into guinea-pigs as follows:

No.	Date of second injection.	First injection.	Site.	Interval.	Second injection.	Site.	Result.	Remarks.
1	8-18-10	10 c.c. condensation from blood	Subcutaneous	22 days	1 c.c. calf serum	Intraperitoneum	No symptoms	Negative.
2	8-18-10	10 c.c. same	Subcutaneous	22 days	1 c.c. same	Intraperitoneum	No symptoms	Negative.
4	8-18-10	10 c.c. same	Subcutaneous	22 days	1 c.c. same	Intraperitoneum	No symptoms	Negative.

SUMMARY AND DISCUSSION

Through the reaction of anaphylaxis the presence of organic matter has been demonstrated in the expired breath.

In brief the method consisted in condensing the moisture from the expired breath of man and injecting the liquid so obtained into guinea-pigs. After a suitable interval (at least two weeks) the guinea-pigs were injected with normal human blood serum. Ninety-nine guinea-pigs were thus tested in twenty-five different experiments. Of the 99 guinea-pigs, 26 gave definite symptoms of anaphylaxis; this does not include the animals showing suggestive or mild symptoms. In four of the animals the reaction was so severe that death ensued from anaphylactic shock.

The expired breath of 8 persons was tested; of these 5 gave positive reactions; upon each of the remaining 3 only 1 experiment was made.

This organic matter must, according to the interpretations of our knowledge of anaphylaxis in the guinea-pig, be protein in nature. Guinea-pigs may be sensitized only with protein substances higher in the scale (that is, more complex) than the peptones.

Further, this protein substance is specific and for the present it is assumed to come from the blood.

The indications are that this organic matter is probably present

in variable amounts, although the reaction is a qualitative and not a quantitative test.

The fact that a number of our experiments resulted negatively may mean either that the organic matter is present in the expired air in exceedingly small amounts or that the guinea-pigs with which we worked did not come from a very sensitive race. There are indications in our work which suggest that the expired breath from certain persons contains more organic matter than from other persons; also that the amount varies with conditions. We obtained a greater percentage of reactions in the guinea-pigs injected with the liquid condensed from the expired breath of females than those injected with the liquid condensed from the expired breath of males. Whether this is a mere coincidence or not may be determined only by collecting more extensive data.

We record a few experiments to determine the effect of time, temperature, acids, and alkalies upon the organic matter in the expired breath, but the data are too limited to draw conclusions. It is of practical importance to collect further information along these lines. It would also be interesting to study the organic matter in the expired breath in health and disease; in different ages, etc.

Every possible precaution was taken to prevent contamination with human protein. All glassware was cleaned with chromic and sulphuric acids, and baked at a high temperature for several hours. In most instances the syringe barrels and needles were new. Rubber gloves were worn at the first injection and other precautions taken. Special measures, such as traps, filters, etc., were provided to eliminate saliva and particulate matters. That these devices were successful is proved by the fact that the condensed liquid usually showed no growth when inoculated into culture media. Control experiments noted in the text were used to check the technique.

A comparatively large number of the guinea-pigs inoculated subcutaneously with the condensed liquid from the expired breath developed sloughs at the site of the injection. It is not certain whether this was due to the pressure of the relatively large amounts of liquid injected or to some irritating principle contained in the liquid. Occasionally the local effects may have been due

to the fact that the liquid was cold when injected. The injection of the condensed liquid caused no other untoward symptoms upon the animals, which is quite contrary to the observation upon rabbits of Brown-Séquard and others.

The best results were obtained when the second injection was given directly into the heart. With a little practice this operation upon the guinea-pig is easily performed and unattended with any ill effects. As human blood serum was used it was not convenient to obtain enough of it to test the hypersusceptibility of the guinea-pigs by subcutaneous or peritoneal injections. When the second injection was placed under the dura through the optic foramen the results were sometimes clouded by the appearance of symptoms which were interpreted to be the result of central irritation.

The logical conclusion from our results is that protein substances under certain circumstances may be volatile. It seems unlikely that such a complex molecule should possess the power of passing into the air in a gaseous form. The volatility, however, now in question may resemble that solubility which deals with particles in suspension in a physicochemical state (colloidal suspension). The protein may simply be carried over in "solution" in the watery vapor.

Our experiments are too few to state that albuminous substances such as egg-white, milk, or blood serum *in vitro* is "volatile." However, they are sufficiently suggestive to stimulate further work along this line.

The fact that organic matter is present in the expired breath does not mean that these substances are poisonous. The physiological effects should now be studied. It is evident, however, that the air contains many substances which we cannot at present discern, some of which may have an important bearing upon health. Thus it is well known that most of the cases of sudden death following the first injection of horse serum (diphtheria antitoxin) occur in adults. Children rarely give a severe immediate reaction at the first injection. How the adults become sensitized has always been a mystery. It may now be assumed that some susceptible persons may absorb, through the lungs, enough horse protein, from close association with horses, to become sensitized. This

hypothesis will be tested by exposing guinea-pigs to the expired breath of horses and then testing their power of reaction to horse serum. The expired breath of other animals will be similarly tested and the condensed breath of animals other than man will also be studied.

The fact that the expired breath contains definite amounts of specific organic substances will also have an immediate bearing upon the problems of ventilation and the effects of vitiated air. There has recently been a growing tendency to regard the ill effects of vitiated air as due to the increased temperature and moisture, but it is now apparent that there are other factors which must be taken into account.

DISCUSSION

Dr. S. J. Meltzer: I would suggest that the proteid originates from the broken-down ciliated epithelium.

Dr. Rosenau: That may well be.

A COMPARISON OF PHYSICAL SIGNS AND X-RAY PICTURES OF THE CHEST IN EARLY STAGES OF TUBERCULOSIS

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General Consideration of Thoracic Acoustics. Within the last year it has occurred to one of us to become acutely impressed with the necessity of making an absolute diagnosis in a series of cases presenting rational evidences of pulmonary tuberculosis. Physical examination of these persons disclosed none of the signs usually depended on for the apprehension of incipient lung disease, but the clinical history of lessened energy, susceptibility to fatigue, digestive disturbance, occasional afternoon temperatures, and various other accompaniments of failing health plainly indicated a serious constitutional disturbance which, if tubercular, implied an active undermining of powers which it was of vital importance to check at once. Fortunately, at this time there was under observation a patient whose chest was negative to even expert examination—pursued along general lines — although tubercle bacilli had for a while appeared in his sputum a few months previously and his clinical condition remained very unstable. A careful study was made of this patient to determine whether any definite physical signs were associated with the advent of tuberculous infiltrations. The results were positive to a gratifying degree. It was found that changes in the resonance of voice or whisper could be detected by stethoscopic auscultation when the alterations of physical structure within the

chest eluded other means of examination. The auscultatory changes referred to included an estimation of the quality, the intensity, the pitch, and especially the duration of the audible vibrations, as well as their distribution over the chest. Obviously, nothing new is contained in these mere statements; nevertheless, the writer can certify that in his own experience a special study of physical diagnosis through many years has failed to achieve a tithe of the certainty in the detection of minute changes in the lungs which the proper application of this method confers. From the theoretical point of view it is obvious that the acoustic phenomena of the chest must respond to every alteration in the thoracic contents. It only remains for practical purposes to discriminate the vocal attributes of definite organic changes.

The vibrations of the vocal cords which produce voice are transmitted in all directions with an intensity dependent on the continuity and elastic properties of the conducting tissue. The air stream passing through the glottis takes up the vibrations of the cords and, according to the shape and size of the air chambers above, one or another group of the partial tones contained in the laryngeal note is magnified by sympathetic resonance, giving rise to the varied vowel sounds characterizing the voice. The property of elastic bodies to magnify sound by sympathetic vibration is of fundamental importance in the apprehension of the physical signs of the chest. It seems obvious that the air waves which are excited by tissue vibration, can in turn, when powerful enough, react upon distant tissue and produce or increase vibrations in it, just as a singing voice calls forth a response from the wires and sounding board of an open piano. Thus, a sound heard on auscultating any part of the chest is primarily due to tissue conduction or air transmission of vibrations arising in the larynx. The quality, pitch, and intensity of the sound heard with the stethoscope depend upon the acoustic conductivity and sympathetic resonance of the tissues traversed, and especially upon the resonating and conducting properties of the tissues immediately under the bell of the stethoscope. Thus the examiner can usually declare with confidence the situation of a small superficial excavation anywhere in the lungs, presumably because the cavity forms a veritable resonator for the vibrations reaching it. Again,

the modification of voice and whisper in a limited section of the lung gives evidence of a local intense congestion or consolidation through which distant vibrations are more readily transmitted to the surface. The examiner who listens to the sounds in the chest inevitably tends to ascribe to the visceral conditions upon which his mind is fixed all the auditory phenomena that are manifest. Nevertheless there is a constant source of error, often of considerable magnitude, in the interpretation of thoracic sounds. This consists in the sympathetic vibration of the chest wall itself due to phonation and which in its more exaggerated form appeals to the sense of touch as the "tactile fremitus."

The Acoustics of the Normal Chest. In order to intelligently use the voice and whisper as instruments for the diagnosis of disease the medical examiner must thoroughly apprehend the normal acoustics of the chest. The thorax is a resonator which may be sharply differentiated into two parts—first, the viscera enclosed by the chest wall and, second, the chest wall itself. Manifestly, sounds owing their intensity to mural vibrations have very subordinate interest for one who investigates the properties of the underlying viscera; they can but disturb and distract the attention; but by the ordinary mode of auscultation they are inseparable from the visceral vibrations. Fortunately there is an extremely simple and effective method of annulling the sounds intrinsic to the chest wall while leaving unaffected those pertaining to underlying structures. The principles of this method were expounded by one of us many years ago, with special reference to the sounds of the heart.[1] If auscultation be performed with the ordinary binaural stethoscope, whose chest- and ear-pieces are connected by plain rubber tubes and which therefore transmit by pure air conduction, and the bell of the instrument is laid very gently upon the skin, there is brought to the ear the combined resonance of parietes and viscera. Let now the bell of the instrument be pressed very firmly against the chest wall and sound due to sympathetic vibrations in the latter is completely blotted out and the attention may be fixed unconfused upon the acoustics of the underlying viscera whose alterations alone are of clinical

[1] Sewall, On the Use of Stethoscopic Pressure in Physical Examination of the Heart, New York Med. Jour., 1897, lxvi.

importance. The reader must test this maneuver at the *base* of a normal chest during vocalization to be impressed with the predominance of mural vibrations in our estimate of the vocal characters of that region. The more powerful the vocal resonance, as indicated by tactile fremitus, the more astonishing is the damping effect of stethoscopic pressure. In the same manner powerful, echoing resonance heard on gentle contact with the *manubrium sterni* may often be completely annulled by firm pressure through the chest-piece; that is, the sternum is a sounding board which has given factitious power to the vibrations from below. When the sound is not thus damped the fact is significant of abnormal underlying conducting media between trachea and breast bone. There are two qualitative modifications of the ordinary vocal resonance which deserve specific mention. In the first the sound is of a deep, powerful drum-like "resonant," "chest tone." It is accompanied by a good deal of tactile fremitus and is specially developed in healthy vigorous young men. This resonance belongs almost wholly to the chest wall, and is, especially over the lower parts of the lungs, nearly obliterated by stethoscopic pressure. The second form of resonance has quite a different quality and has been characterized by the writer as a "ringing bronchophony." It is suggestive of the tones of a soprano voice in its middle register.

Its typical characters are developed most strikingly in the chests of young females. In the writer's opinion the apprehension of this form of bronchophony is of extraordinary diagnostic importance, because it is due not so much to parietal as to visceral vibration, for often it is well-nigh undiminished by stethoscopic pressure; on the contrary, in the conditions noted below, pressure with the stethoscope is apt to render plainer and *bring nearer the ear* the ringing bronchophony; especially is this the case over the upper half of the lungs. Moreover, the ringing bronchophony is, according to the results of the present investigation, the very earliest sign of a pulmonary change of fundamental importance—namely, vascular congestion, which is possibly combined with a degree of atelectasis. Time and again in this investigation the diagnosis of abnormal vascular congestion has been made as to the lungs of clinically healthy subjects and has been verified by the completely indepen-

dent interpretation of the *x*-ray picture of the chest. Deferring for the present further discussing of vocal resonance in the normal and clinically normal chest, let us consider the acoustic significance of transmitted whisper.

It is a matter of elementary knowledge that whispered sounds have a very restricted distribution through the normal chest and that their extension or change in quality and intensity is one of the surest indications of a pathological condition. It is here maintained that the special importance of the auscultated whisper is that its transmission is a result of purely visceral conduction and resonance. Mural vibrations usually take no part in the sound. There are two obvious explanations for this fact: first, the relatively low intensity of whispered sound; second, whisper is *noise* due to non-periodic vibrations; sympathetic resonance is fundamentally dependent on periodic vibrations such as make up musical tones. Therefore, except in very few special cases, pressure with the stethoscope does not annul the whispered sound; on the contrary this is thereby made clearer and brought, as it were, nearer the ear, probably by reason of the damping of associated adventitious parietal vibrations. Numerous abnormalities within the thorax modify the intensity, quality, and transmission of whispered sound, but one of the most interesting and important is the condition of what is probably intense, acute pulmonary congestion, such as precedes actual consolidation of the lung. During the prevalence of influenza the last winter the writer had many opportunities of tracing the erratic course of vascular congestion reactive to the infection. These areas of abnormal vascularization show a sharply limited transmitted whisper; in a more advanced stage there may be added an audible expiratory murmur of elevated pitch, and both may pass away without the onset of percussion dulness, etc., indicative of actual consolidation. Skiagrams of the chest in appropriate cases show the negatives to be covered with a more or less dense mist in the regions of transmitted whisper. We are inclined to believe, as illustrated in Fig. 2, that the shadow is due to crowding together of the pulmonary capillaries, as well as to the relatively diminished volume of the air cells. This abnormal transmission of whisper in acute disorders indicates a stage of vascular congestion somewhat

more advanced than that which may be detected through the "ringing bronchophony." The two signs may occur together or the latter may be found alone. That the increased conductivity which exaggerates the whisper is due rather to congestion than to atelectasis in the lung tissue is indicated by the fact that whispered sound is more intense to auscultation when produced in the phase of extreme inspiration than in that of extreme expiration. The writer has not been able to detect the abnormally transmitted whisper in cases of simple bronchitis and therefore ventures the suggestion, only, that we have in its occurrence a specific means of distinguishing between congestion of the pulmonary vessels from the right side of the heart and of the bronchial vessels from the left side.

Topographical Distribution of Voice and Whisper through the Normal Chest. It was suggested by Goldscheider[1] and made very clear by Fetterolf[2] that the sounds auscultated at the apices of the lungs were, for the most part, transmitted transversely directly from the trachea. The normal auscultatory differences between the apices is attributed by Fetterolf to the peculiar anatomical relations of the two apices to the trachea. This air tube lies in direct contact with the inner wall of the right apex while it is separated from the left apex by a considerable thickness of indifferent tissue. The view that apical vibrations are due to direct conduction from the trachea had been reached independently by one of us and has been carried out to its legitimate consequences with interesting results. There is a natural acoustic topographical division of the lungs into two parts, an upper and a lower, according to their relations to the trachea and two main bronchi. The upper parts of the lungs receive, particularly on the right side, vibrations directly from the walls of the great air vessels, so that the intensity of conducted sound as well as the vigor of sympathetic vibration is greatly enhanced in the corresponding region of the chest. This natural acoustic division in the lungs is not striking with the ordinary method of auscultation but becomes very obvious when the principle of stethoscopic pressure is applied.

[1] Ueber die physikalische Frühdiagnose der Lungenschwindsucht, Zeitsch. f. klin. Med., 1909, Band lxix, S. 205.

[2] The Anatomical Explanation of the Greater Amount of Vocal Fremitus and Vocal Resonance Normally Found at the Apex of the Right Lung, Archives of Int. Med., 1909, iii, 23.

Listening over the lower parts of the normal lung, the resonance, no matter how powerful, is almost completely abolished by firm pressure on the stethoscope. As the instrument explores the front of the chest upward the same result is developed by pressure until it reaches, on the right side, approximately the top of the fourth rib or, on the left, the bottom of the third rib, then quite suddenly the voice sounds persist in great measure no matter what the degree of stethoscopic pressure. The result is easily explained by admitting that the "bronchophony" of the lungs below the fourth ribs in front is almost wholly the sound produced by sympathetic resonance of the chest wall itself. The persistence of voice sound with pressure in the upper chest is obviously dependent not on mural resonance but on direct conduction of vibrations from the contiguous trachea and bronchi. Practically the same acoustic differentiation can be made on the posterior chest wall. The dividing line between upper and lower divisions runs across the back at a point somewhat below the inner ends of the spines of the scapulæ in a situation nearest the roots of the lungs. The acoustic topography in the back is not so sharply defined as in front by reason of the influence of the large descending bronchial branches, the direct vibrations from which are apt to reach the chest wall as low down as the angles of the scapulæ. The examiner will find, of course, that normally all sounds in the upper chest have greatest intensity near the middle line and become weaker toward the lateral margins. It may be mentioned as an extraneous matter that the respiratory murmur itself is intimately related to the parietal resonance of the chest, but this phase of the subject has not yet been definitely investigated.

The Method of Physical Examination. The patient was examined sitting, with chest bare, by one of us employing the ordinary methods, inspection, palpation, etc., winding up with a detailed study of the distribution, intensity, quality, and prolongation or echoing characters of voice and whisper. All results were definitely recorded in writing. The subject was then *x*-rayed by the other of us, who dictated a detailed description of the plate, summing up with a diagnosis based on the skiagram. The two descriptions and diagnoses were then compared. In the auscultation the subject was asked to pronounce, first by voice and later by whisper, the

syllables "one, two, three," and particular attention was paid to the prolongation of the sound from one syllable to the other and to its alteration in quality. No better illustration of the acoustics of the diseased lung can be offered than in the sounds which may be heard in every normal person when the bell of the stethoscope is applied to the back of the neck, high up, or even to the posterior part of the skull. The tones heard here are prolonged, echoing and altered in quality to a degree which is but faintly imitated in the early stages of tuberculosis of the lungs.

In the normal subject bronchial resonance, more or less persisting under stethoscopic pressure, is noted in front, on the right to about the fourth rib, on the left to about the third rib. The whisper, if gentle, reaches on the right scarcely below the first intercostal space and on the left is confined to the inner half of the same. The persistence of the whisper down along the borders of the sternum is suspicious of disease, and isolated areas of prolonged or intensified voice or whisper are certain evidences of physical abnormalities in the chest. As said before, whispered sound is retained during stethoscopic pressure except over the sternum when this acts as a sounding board. Posteriorly, the acoustic phenomena of the regions above and included between the scapular spines differentiate these parts from those below. On the right vocal resonance is more or less marked throughout the region, gradually fading laterally and below. An echoing character to the sound, especially in an isolated area, and if retained and made more distinct with pressure is most significant of pathological change. The whisper should be confined to about the inner half of the right apex; if widely diffused, concentrated in an isolated area or prolonged, it is significant of pulmonary infiltration. On the left the bronchophony is higher pitched and less intense, and is apt to reach not so low as on the right. The whisper on the left is normally confined to the upper inner corner of the apex.

It must be granted that the study of the chest according to this method presupposes on the part of the examiner a clear mental picture of the normal acoustic ranges, but a similar qualification is demanded of the expert in every field of physical diagnosis. In the writer's experience this method of *acoustic diagnosis* is much easier to carry out and more certain in its results than the light

"finger-finger" percussion employed with such success by Goldscheider[1] in detecting apical changes. The method also is applicable over all parts of the chest and is not limited, like the latter, to the upper portion. Knowing the normal acoustic characters of the apices, it requires but little time or effort to apprehend the signs of disease. A bronchophony ever so slightly metallic and echoing, rendered more distinct and nearer the ear by pressure, denotes a pathological condition in the lung. A whisper distributed unduly widely, especially if prolonged, signifies the same thing. The discrimination of the nature of the pathologic change into congestion, consolidation, excavation, etc., is a matter of detail which does not concern us here.

Diagnosis by Means of X-rays. All examinations were made skiagraphically with the subject stripped to the waist and lying prone with the scapulæ thrown well outward. The antikathode was centred over the spine of the fifth dorsal vertebra (opposite the junction of the second rib with the sternum) and at a distance of 25 inches from the plate. The earlier pictures were made with the use of a coil and exposures of five to ten seconds; the later with a transformer and exposures of one-half to two seconds.

The later plates were much the more satisfactory. As it was our special object to determine the skiagraphic signs of the earliest stages of pulmonary tuberculosis and to compare them with the results of physical examination, three classes of subjects engaged our particular attention: (1) Completely normal; (2) those suspected of incipient tuberculosis; (3) those certainly afflicted with tuberculosis but presenting doubtful morbid signs to ordinary physical examination. Plates from such cases were compared with those from a considerable series of subjects with more or less advanced tubercular infection as well as with various chronic non-tubercular affections of the chest. Our conclusions are founded upon the study of 101 cases varying in age from five to fifty-nine years; 50 males and 51 females. Besides there were considered a considerable number of plates the originals of which were not submitted to physical examination. The extensive literature on thoracic skiagraphy has not yielded to us a wholly satisfactory

[1] Loc. cit.

description of the normal chest negative. In fact, we have come to conclude that the "normal" chest, from the *x*-ray viewpoint, is, at least in the adult, well-nigh an ideal. A person may be clinically perfectly well while the Röntgenogram of his chest shows structural changes of pathologic nature. This should be anticipated when we consider that the *x*-ray plate reveals the optically indelible marks of every physiological struggle which the thoracic viscera have survived. ' It seems to be the general opinion of investigators that the ordinary contents of the thorax are more or less opaque to the *x*-rays somewhat in the following order: (1) Deposits of lime—as in calcified glands; (2) bone; (3) altered lymph nodes; (4) blood; (5) fibrous tissue; (6) muscular tissue. It is generally agreed that normal lymph nodes and early tubercles cast no shadow. The same may be said of mucoid secretions which may give rise to abundant rales.

The Negative Plate of the Normal Chest. It is an obvious but important consideration that the technical preparation of the negative largely determines the configurations which it will reveal. In order to distinguish between the dense shadows of the mediastinum, for example, the finer lines in the body of the lung are washed away. The technical skill of the Röntgenologist is determined by his choice and use of apparatus best designed to differentiate coarse structures while preserving the details of delicate figures. It is also obvious that the sharpness of outline and apparent density of objects which cast shadows are increased in proportion to their proximity to the plate. Thus a calcified area in a costal cartilage casts a dense and well-defined shadow when the subject lies prone upon the plate, while the same object may be ill-defined and hazy if the subject lies upon his back. Therefore, pictures of the same lungs may show very different details of structure, especially in diseased conditions, according as the plate has been exposed at the front or back of the chest.

In the more or less uniformly dense shadow of the normal mediastinum, three distinct intensifications of the opacity can be brought out. The topmost obviously is caused by the arch of the aorta, which toward its descent is seen in optical section. The middle one, situated within the base of the heart, we believe to be due

chiefly to optical section of the pulmonary artery. The lowermost shadow seems to be seated on the diaphragm and its causation is more problematical. The lateral borders of the mediastinum vary greatly in definiteness, especially on the right side. When the outlines are clear cut, which is especially true in cases of disease in which the mediastinum is broadened, it appears as if the boundaries of the region must be made by the dense, fat-infiltrated, median pleuropericardial membranes seen in optical section. The extreme upper left hand corner of the mediastinum is sharply outlined by a dense shadow which obviously represents the arch of the aorta and projects as a more or less prominent circular segment which has no doubt frequently been misinterpreted as an aneurysmal dilatation. The left outline of the descending aorta inclines inward from the arch and is usually lost in the shadow of the spine at about the level of the seventh dorsal vertebra. In a few pictures, mostly when taken in extreme inspiration, the outlines of the ascending aorta may be traced rising from the base of the heart and passing up outside the right border of the vertebral column (Fig. 1), but usually this part of the aortic arch is hidden within the shadow of the spine. With the antikathode situated as described the summit of the aortic arch should about correspond with the lower edge of the sternal attachment of the clavicles. A constant veil-like or sometimes rather dense shadow forms a strip some two-thirds of an inch in width and extends, tangent to the spine, from the inner, lower border of the right clavicle to the superior outline of the right side of the heart in which it terminates after apparently bending somewhat inward. This shadow is usually, and probably correctly, ascribed to the superior vena cava. It may be intensified by the shadows of the ascending aorta and the root of the right lung. The shadow of the heart does not particularly concern us here and the special consideration of its extraordinary variations is reserved for another communication.

The trachea is readily recognized as a dark streak half an inch or more wide, with whitish edges, running down the upper spine more or less to the right of the median line and usually inclining decidedly to the right after entering the thorax. The main right bronchus is clearly distinguished, leaving the trachea at a very oblique angle;

it enters the root of the lung from its mesial side, and frequently radial dark streaks, lesser bronchi, spring from its extremity within the hilus and reach to the diaphragm and far toward the outer confines of the lung. Surrounding the main right bronchus, chiefly on its outer border, is one of the most characteristic, variable, and important skiagraphic features of the chest.

It is the shadow of the hilus or root of the right lung. Its outer margin reaches about one and a half inches to the right of the spine, and its upper and lower borders are commonly included between the lower margin of the sixth and the upper margin of the eighth ribs posteriorly. But variations in the area and the structural characters of the root form perhaps the most striking features of early pathological changes in the lung. Between the bronchus and the vertebral shadow the root is usually represented on the negative as a more or less dense, homogeneous cloud, though in development of the plate this space may be cleared so that the portion of the root inclosing and external to the bronchus may be separated from the mediastinal shadow by a dark band. The root external to the bronchus varies indefinitely in its structure. In the normal subject it resembles somewhat a semitransparent cirrus cloud which may be homogeneous or crossed with more opaque streaks or mottled with denser nodules, and it is traversed with dark areas which evidently represent longitudinal or optical sections of the bronchial branches. In the more successful negatives well outlined homogeneous shadows run through the root and can hardly be anything but the larger bloodvessels (Fig. 1). Of all our negatives perhaps the most instructive were those taken from two subjects, both young men of twenty-five and twenty-nine years respectively, one of whom was in all respects normal and the other presented to physical examination slight suspicion of apical infiltration. Negatives were made of these subjects in various phases of respiration.

In forced expiration, in which the expiratory effort was continued with the nostrils pinched together at the end of deep expiration, the general field of the lung was shadowed, evidently by the crowding together of the minute bloodvessels, as well as by compression of the air cells; the apices were brought well into view by depression of the clavicles and their vessels were injected (Fig. 2).

Especially interesting were the pictures taken at the end of deep inspiration, the inspiratory effort being continued with nose and mouth closed for several seconds before exposure. In these negatives the ramifications of the vascular tree were well-defined throughout the lungs and at the same time the divisions of the bronchial air tubes were clearly indicated. The root of the right lung in one of the pictures (Fig. 1) was manifestly made up of a great vascular trunk from which clearly defined branches could be traced, breaking into finer and finer divisions, to the outskirts of the lung. On most plates the root area is coarsely mottled with more or less diffuse opacities varying from one-eighth to one-half inch in diameter, and in cases of tubercular disease, or of older "normal" subjects, very dense circular or irregular shadows, usually not exceeding one-fourth inch in diameter, may be scattered through the roots.

The radiographer is apt to confidently define these denser concretions as calcified glands, and such they probably are. In a negative taken during deep inspiration we found a cluster of four tiny very dense nodules typical of calcification. In two other plates from the same subject, one taken in deep expiration and the other in moderate inspiration, the same nodules were recognized, but appeared diffuse, as do the shadows of small bloodvessels. The interpretation of less dense and more diffuse opacities is chiefly guesswork. They usually represent either pathological lymph nodes or bloodvessels in more or less optical section. The beginner in such diagnoses is apt to class them all as bronchial glands, but with riper experience he is almost equally inclined to consider them to represent bloodvessels seen in optical section. For our part we think that the homogeneity of the nodular shadow, with a density decreasing from the centre, stands for its vascular origin, while internal differentiation or irregularity of outline of a markedly dense shadow signifies glandular infiltration; each case must be judged by itself. The main left bronchus, less often seen than the right, takes a course more nearly horizontal than the latter. The hilus shadow which surrounds it is therefore somewhat elevated and displaced to the left.

The root of the left lung is apt to be obscured by what we take to

be the pleuropericardial membrane which forms the left border of the mediastinum. It is usually more homogeneously cloudy and less clearly differentiated in structure than the right root, probably because of its closer contact with the pulsatile structures of the mediastinum. Just outside the lower border of this root it is common to find opaque, diffuse masses of probably vascular origin, and these are habitually interspersed with four or five well-defined dark, circular, or elongated areas which undoubtedly represent the sections of a cluster of bronchi, since they persist in plates of the same chest taken in states of extreme inspiration and forced expiration. Furthermore, as the physical examination at times determines, a well-marked isolated echo of voice and whisper in the nearest area on the front of the left chest, between the third and fourth left costal cartilages, it may be assumed that such bronchi occasionally incline forward from the root. Less constantly, in our plates, in a similar area in the right lung, that is, outside the lower margin of the root, a group of circular shadows, apparently bronchi, can likewise be made out. In certain degrees of pulmonary fibrosis the circular dark areas, which we interpret as optical sections of bronchi, are numerous and widely distributed through the lungs. Radiating from the roots of the lungs are the branches of the "bronchial tree." We have been accustomed to group them as lower vertical, lower oblique, lateral, upper oblique, and upper vertical; the oblique being usually offshoots from the vertical radiations. Seldom have we found the well-marked differentiation of three main stems on the right as distinguished from two on the left as described by Dunham and his coworkers.[1] The radiations on the left, especially in the lower part of the lung, have a diffuseness and homogeneity which distinguishes them from the sharply defined figures on the right, although some of our plates show them equally as clear cut. Dunham's explanation of this difference as being due to the greater influence of cardiac pulsation on the left side can hardly be questioned. The radiations proceed from the root branching into finer and finer offshoots forming a

[1] Dunham, Boardman, and Wolman, The Stereoscopic *X*-ray Examination of the Chest, with Special Reference to the Diagnosis of Pulmonary Tuberculosis, Bull. of the Johns Hopkins Hosp., July, 1911, p. 229.

tangled network which in the best negatives is visible to the extreme confines of the chest. The vertical, ascending and descending, are usually much more prominent than the lateral radiations. Circumscribed within the radiations are circular dots of considerable opacity which manifestly, in many cases at least, represent the optical sections of vascular offshoots from the parent bloodvessel. We do not enter the still vigorous debate as to the anatomical origin of the so-called "bronchial tree," but maintain that in the negative of the normal lung of the youthful subject the opaque radial shadows are wholly, or nearly wholly, of blood-vascular origin, while the dark streaks represent ramifying bronchi. A structural mark of the hemic origin of a radial shadow seems to us to consist in the homogeneity of the shadow.

In older subjects and in lungs altered by disease it is common to find sharply double-contoured radiations inclosing an unshadowed core; these are probably bronchi. In such radiations specially dense and often irregular concretions are numerous and have been defined by us as fibroid or calcareous glands. Little doubt can exist that a specially dense shadow occurring isolated in a dark field and of greater diameter than the radiations about it is, even in the "normal" subject, due to a glandular concretion. Radiographic study of the apices of the lungs, so important in considering the early changes in tuberculosis, should engage a special arrangement of plate and table. In our work a uniform faintly "ground-glass" appearance of the apices was presumed to be normal. It is common to find the internal half of each apex traversed by delicate fibrils which are continuations of the vertical radiations from the root, and the whole field may be softly stippled with what are evidently vascular nodules. A fine network of what we interpret as vascular lines is sometimes seen throughout the field of the apex in young subjects (Fig. 3). This appearance is probably typical of incipient apical tuberculosis; it is probably preceded by the stippled condition referred to above. The configurations in the apex closely resemble those, undoubtedly of vascular origin, which appear in the inferior lappets of the expanded lung where it fills in the space made by retreat of the diaphragm from the chest wall (Fig. 1). The lower half of the left lung is usually deficient in the network

configuration conspicuous on the right side, possibly because the vertical elements of the arborization are blurred by the pulsations of the heart. Not infrequently large unshadowed areas or clefts may appear upon a plate showing otherwise good general detail of configurations. They are doubtless due to the fact that, especially in the phase of inspiration, certain sagittal sections of the lung are relatively free from opaque structures.

As an interesting side issue, attention may be called to the extraordinary lateral compression of the liver which results from vigorous inspiratory contraction of the diaphragm. Such massage must be of extraordinary moment to the circulation (Figs. 1 and 2). To conclude this description of the normal lung negative, we think that the configurations in the skiagram of the lungs of a youth free from history of chest disease are almost altogether of vascular origin. Nevertheless, in the neighborhood of the hilus a bronchus seen in optical section may occasionally have its circumference indicated by a definite ring (as in the right hilus of Fig. 1). As age increases, especially in subjects who have habitually breathed in a dusty atmosphere, the roots and radiations of the lungs exhibit concretions and intensified streaks which at present are interpreted by us as resulting from deposits in the bronchial glands and from peribronchial fibrosis. In the healthy lung all collections of dense shadows are in immediate relation with the root.

The Skiagram of the Tuberculous Lung. In the advanced case of tuberculosis the picture differs so widely from the normal as to appear to be characteristic of the disease, yet we have not been able to distinguish in the *x*-ray plates such cases from that of a patient who succumbed to a lung disease of undetermined nature in which sputum examination remained for years negative as to tubercle bacilli. A presumably non-tubercular stonecutter furnished a skiagram in which, except for the relatively moderate involvement of the apices, the mineral deposits occasioned opacities resembling the densest of tubercular structures. The negative of the lung in advanced tuberculosis shows usually most marked changes at the apices and upper lobes. More or less dense masses of shadow occur throughout the affected portion. A very characteristic appearance is the loss or diminution of radiations between such shadows and

the root of the lung, and a separation of the shadowed areas from the general scheme of arborization. It is to be suspected that the *x*-ray diagnosis of early incipient cases of tuberculosis has usually been attempted from the viewpoint of this morbid picture rather than from that of the normal one. Before attempting to designate the Röntgenographic criteria of incipient tuberculosis it will be profitable to consider from an *a priori* standpoint what changes the skiagram in such a condition should be expected to show. It is generally admitted that fresh, newly formed tubercles cast no shadows in the *x*-rays. Max Cohn,[1] who has devoted special study to the subject, declares that the characteristic mottling found on the negatives in cases of acute miliary tuberculosis is due not to the tubercles themselves, but arises from the intense vascular engorgement accompanying the condition. A case of our own has impressed us with the correctness of this conclusion. We can set no limit to the interval between the formation of the tubercle and the development within it and in the surrounding tissues of such physical changes as will block the *x*-rays and cast a shadow. It may well be that in tuberculous tissue opacity to the rays may be long delayed after the advent of clinical tuberculosis, which is essentially a chemical-physiological phenomenon. If the Röntgen-rays, then, are to aid in the early diagnosis of pulmonary tuberculosis it must be chiefly or largely through their ability to differentiate vascularities in the lungs. In their excellent paper Dunham[2] and his coworkers think they have distinguished a pathognomonic sign of early tubercular infections in the delicate arborization of fine lines frequently seen in the negatives from cases of incipient tuberculosis. If we have rightly apprehended their description we must ascribe this configuration to a vascular engorgement which cannot, strictly speaking, be considered of itself alone as pathognomonic of tuberculosis. If changes in vascular congestion connote the incipient stage of tubercular infiltration their recognition must be determined by comparison with the normal circulation pictures. We shall return to this subject later.

[1] Die Anatomische Bedeutung der Lungenröntgenogramme und ihre Beziehungen zur Röntgendiagnostik der Lungentuberkulose, Zeitsch. f. Tuberkulose, April, 1911, Band xvii, S. 217.

[2] Loc. cit.

Fig. 1.—Male, aged 25. Supposedly normal case; v. Pirquet test negative, but physical examination revealed slight crackling at left apex and rough murmur at right. The negative was taken in the phase of deep inspiration, the effort to inspire being continued with nose and mouth closed. The vessels are markedly injected with blood and the bronchi with air. Note the suspicious area of congestion in the upper, outer half of left lung. The print illustrates the plainly vascular constitution of the normal right hilus. Note also the shadow of the ascending aorta blending with that of the superior vena cava on the right of the mediastinum.

Fig. 2.—Same, supposedly normal, subject as Fig. 1, but the negative was taken in the phase of forced expiration, the effort being continued with nose and mouth closed. Note the diffuse shadow covering both lungs due to crowding together of pulmonary capillaries. Apparently distended bronchi are seen outside each hilus. The larger bloodvessels are compressed and obscured. The sign of abnormal congestion below the left clavicle still persists. The greater congestion of the right apex is of doubtful significance.

Fig. 3.—Female, aged about 28. Early incipient tuberculosis, evidenced by clinical history and physical signs; no sputum. Note the fine, isolated network in the right apex, and the stippling above the left clavicle. There is a somewhat isolated area of congestion on the left extending downward from the first intercostal space, anteriorly (the shadow here is somewhat intensified by that of the breast).

FIG. 4.—Female, aged 30. Patient well, clinically, and not aware of her condition. Has improved greatly in last six months after very slow convalescence from "typhoid fever." She has well-marked, probably healed, tuberculosis of left apex extending to second rib in front and nearly completely isolated from radiations. A similar condition is seen on the right under the first rib anteriorly. There is a general increased vascularity of right lung dissociated from radiations, with scattered opacities which probably represent altered lymph-nodes.

FIG. 5.—Male, aged about 36. Arrested tuberculosis. Infiltration at each apex, most marked on right. An isolated tuberculous deposit occurs in outer part of left second intercostal space, anteriorly. The finer fibrillations are thought to represent bronchial fibrosis. Note the group of apparent bronchi, in optical section, just outside root of left lung. Note the comparative dissociation of infiltrated areas from the hilus radiations.

The apex of the normal lung has usually appeared on our negatives as a uniformly unshadowed or slightly "ground-glass" field without configurations. But it is common to find linear extensions of the vertical radiations from the root penetrating and traversing the inner portion of the apex, especially on the right side. These are usually taken for normal figures; nevertheless, it is well to bear in mind the careful work of F. W. Jones[1] who advances the hypothesis that infection of the right apex arises from direct contact with the main right trunk of the thoracic duct in which the tuberculous process starts. The local changes in such a process should be impressed on the negative. Occasionally, and especially in undoubted cases of tuberculosis, the linear streaks are not confined to the inner part of the apex, but this whole region is occupied by a network of similar fine lines running in all directions; more commonly still a soft stippling is imparted to the area.

A study of our negatives leads to the conclusion that this appearance of an isolated vascular network in the apices is typical of a condition which, occurring anywhere in the lungs, is indicative of a focus of tubercular irritation. In the normal lung picture the arborizations are wont to have a characteristic regularity. The size of the trunks diminishes regularly from their origin at the hilus and their branches break up into finer and finer twigs which interlace, more conspicuously in the right lung, and the network becomes more delicate until lost in the periphery.

Such a regularity of arborization is still maintained in the greatly intensified configurations presented in non-tubercular cases having symptoms of chronic bronchitis with asthma and in which fibroid changes in the lungs, with more or less pneumonokoniasis are suspected, though we are inclined to think that the discrete masses found in the lungs in cases of "miners' consumption" may likewise occur dissociated from the radial figures. The evidence leads to the suspicion that isolated patches of accentuated vascularity, not directly related to the radial vessels springing from the hilus, are the very earliest pathognomonic skiagraphic signs of tubercularization of the lung tissue.

[1] An Anatomical Inquiry into the Pathway of Tubercular Infection, Lancet, April 2, 1910, p. 94.

A still earlier skiagraphic evidence of tuberculosis which, however, does not appear to us to be specific of the disease is an increase of vascular congestion denoted by thickening of the vessels supplying the affected areas which themselves are hyperemic. Both Levy-Dorn and Cornet[1] and Dunham[2] call attention to the same appearance. This thickening of the main trunk connecting the hilus with the tuberculous area may be noted in an old case of disease in which activity is renewed; but, as pointed out above, we believe the characteristic tubercular picture tends to preserve the peripheral network while more or less eliminating the radial stem from which it arose. It is as if the infecting seed transported to a peripheral area had there multiplied independently.

It is impossible to determine from the *x*-ray negative at what period the area of localized congestion, which we think the earliest sign of parenchymal tuberculosis, begins to show the shadows of tubercular deposits *per se*. In old tuberculous infiltrations one can only surmise, often, which shadows are due to pathological deposits and which to vascular congestions.

If these parenchymal vascular changes have any relation to early tubercular infiltration it must be conceded that they characterize the lower portions of the lung scarcely less than those pertaining to the apices. We shall revert to this point later. But it is the appearance of the hilus regions which especially attracts the eye in the Röntgen negative. Increase in the area of the root shadow, alterations in the apparent consistency of its matrix, nodular condensations which are inevitably referred to glandular changes, are common when the rest of the lung presents nothing abnormal. Hence it is the common view of radiologists that tubercular infection begins at the root of the lung, while pathologists are generally agreed that, at least in adults, the disorder arises at the apices. We cannot but suspect that both opinions are formed on facts whose antecedents have escaped observation. We may be permitted to express a provisional hypothesis which these *x*-ray studies have suggested. The suspicion is strong that pulmonary infection usually finds its first seat in the glands at the lung roots. The infection proceeds

[1] Das Röntgenbild des normalen Thorax mit Rücksicht auf die Diagnose der Phthisie, Berl. klin. Wochensch., 25 Mai, 1908, S. 1004.

[2] Loc. cit.

thence in all directions. But the mechanical conditions at the apex are such that the lung in this region has relatively little power to expel the intruding bacillus, which therefore is enabled to settle and reproduce its kind. The instructive experiments of Bacmeister[1] are pertinent in this connection. It is well known that intravenous inoculation of tubercle bacilli may be followed by a general but not a specially apical tuberculosis.

Bacmeister inoculated a series of rabbits through an ear vein with an emulsion of tubercle bacilli. In some of the rabbits he had previously to an extent constricted off the apices of the lungs by a wire twisted about the anterior part of the chest. In these cases isolated, local lung tuberculosis was produced. Further, the elaborate studies of Hart[2] showed that persons having a short first rib, by which the apex is constricted at its junction with the lower lung, are distinctly predisposed to tubercular infection.

X-ray study, in our opinion, gives support not only to a theory of root origin of the infective process, which according to Rieder[3] and others is constant, but to the view that in certain cases the apex is the source of the trouble. In the plates from these cases there is well-marked vascularity at the apex and the root itself is practically normal. But separated from and parallel to its outer circumference is a crown of well-marked opacities which form a distinctive picture.

It may be repeated that in the very earliest cases of tuberculosis nothing more distinctive is portrayed than evidence of increased vascularity, which may be noted in one or both bases as well as in apices and in which areas of congestion tend to occur like nests more or less distinct from the hilus radiations.

These features become more and more pronounced, with the addition of signs of tissue changes, as the clinical course of the disease progresses. The reaction to tuberculin injections, as investigated in numerous German researches[4] would seem to offer crucial evidence

[1] Experimentelle Lungenspitzentuberkulose, 28 Kong. f. d. innere Med., 1911, S. 290.

[2] Die Disposition der Lungenspitzen zur tuberkulösen Phthisie und das Lokalisationsgesetz des Ersten Tuberkulösenherdes, Münch. med. Wochensch., January 19, 1909, S. 123.

[3] Die frühzeitige Erkennung der Lungentuberkulose mit Hilfe der Röntgenschatten, Deutsch. Arch. f. klin. Med., 1909, Band xciv, S. 62.

[4] Fine researches by Schlayer, Deutsch. med. Wochensch., May 14, 1908, Band xxxiv, S. 866; Max Wolff, Berl. klin. Wochensch., January 17, 1910, S. 118 (Abst.,) etc.

of the pathological significance of the skiagraphic changes. This, however, is a false hope, for after a positive tuberculin test we are still in doubt as to whether the reacting focus has been latent or of clinical significance.

It was considered inexpedient to submit our patients to the subcutaneous test, but the v. Pirquet skin test was made in 47 cases. Of these 41 reacted positively, 2 of them only after a second trial, and 6 negatively. In the 41 cases with positive reaction the physical diagnosis of the lungs was negative 10, and doubtful 14 times; the *x*-ray diagnosis was negative 13, and doubtful 15 times. In 2 cases, aged nineteen and twenty years, the skin test was in each twice negative, while the physical and *x*-ray findings were positive. In 2 other cases, aged fifty and twenty-five years, negative to v. Pirquet, our examinations were classed as doubtful. It is probable that with wider experience the length of our "doubtful" list would be considerably reduced.

This investigation has proved so full of suggestion that we regard the careful study of 100 subjects only as the introduction to further research. We have found a general, and frequently surprisingly close, agreement between the conclusions arrived at through physical examination and study of the *x*-ray negative. Though the interpretation of the meaning of morbid physical signs was frequently in error, such signs when found were demonstrated almost invariably on the *x*-ray plate to have a physical basis.

Our general conclusions may be summarized as follows:

1. Auscultation of the voice and whisper affords an exceedingly delicate index of pathological changes in the lungs.

2. Vocal resonance involves vibrations both of the thoracic viscera and of the chest wall. The latter vibrations may be damped and removed from consideration by pressure applied to the bell of the simplest form of air-conducting stethoscope. The whisper, under ordinary conditions, does not evoke the resonance of the parietes; it bespeaks only visceral conditions. It is rendered plainer and brought nearer the ear by stethoscopic pressure.

3. For the purposes of physical examination the lungs are separable into two natural divisions, namely, the parts above, which receive directly the transverse vibrations emanating from the

trachea and larger bronchi; and the parts below, inferior to the third intercostal space in front, which are relatively removed from their influence.

4. With our present ability to produce and interpret *x*-ray pictures, it must be admitted that a judgment founded on clinical history combined with physical signs may lead to a strong suspicion of tubercular infection long before any signs of actual tissue changes, except those involving the bronchial glands, appear on the *x*-ray negative. Nevertheless, we believe that a skiagram of the chest, preferably repeated at not infrequent intervals, is essential to the proper understanding of a patient's condition.

5. Skiagraphic study of the chest resolves itself into two natural divisions: one pertains to the hilus regions, concerning especially the bronchial glands, with their associated peripheral, lymphatic nodes, and the other includes the parenchyma of the lungs itself.

6. Extreme pathological changes in the glands may be recognized with great facility, but alterations of moderate grade need careful judgment in their interpretation.

7. We agree in the view that in the *x*-ray negative of the normal chest the opaque arborizations of the "bronchial tree" are almost wholly composed of shadows cast by bloodvessels. In non-infected subjects the bronchial tree has a typical symmetry and regularity of distribution. It is very suggestive of the shadow of a leafless tree cast by the sun on an asphalt pavement.

8. In practically all our cases of unproved but suspected tuberculosis the skiagraphic negatives exhibited more or less extensive areas of pulmonary congestion, denoted by thicker branches and denser arborizations of the "bronchial tree." As pointed out in the text, such congestion may possibly be recognized clinically by a "ringing" quality of the bronchophony which persists under stethoscopic pressure. We are constrained to believe that the recognition of abnormal congestion has great importance in the early diagnosis of pulmonary tuberculosis. Moreover, since Levy-Dorn and Cornet, Dunham and his colleagues, and ourselves have independently recognized a peculiar vascularization of the lungs in association with tuberculosis, it seems probable that herein exists a specific diagnostic property of the *x*-ray plate.

9. We proceed, however, a step farther and venture the opinion that in tuberculosis of the lungs the earliest pathognomonic skiagraphic sign is the representation of comparatively isolated areas of vascular congestion which increase independently of their connections with the central root. This peripheral focalization of the congestive process and its severance from the main system of vascular radiations are apt to become more and more prominent as the disease progresses and shadow-forming deposits are formed.

DISCUSSION

Dr. W. P. Northrup wished to submit, in discussion, an *x*-ray plate of a young child's chest showing disseminated miliary tuberculosis. One of the profession called it in jest "measles on the lung." This expression well expresses the appearance as shown in the plate. Child, aged ten months, colored, mother robust, father not seen but said to be not very strong. The child had had bronchitis, running ear, and continued temperature, a few slightly enlarged glands in the neck. On entrance a few rales were found at the base of the lungs, the child had fever, was inclined to be mentally dull, seemed to be "sick" out of proportion to the lesions recognized, and tuberculosis was suspected, disseminated. An *x*-ray showed this extraordinary plate picture. Considering the age of the child and the necessitated quick exposure, the plate is thought to be unusually good and illustrating the value in children of chest *x*-ray pictures.

Dr. Henry Koplik: In connection with some recent work on tuberculosis, I had some *x*-rays taken of children who had evident tuberculosis, such cases as acute miliary resulting in tuberculous meningitis and death, with the object of seeing whether we could detect glands and infiltration at the root of the lung. Although we did get some pictures which suggested this condition, I do not think we are in a position to say that we can definitely mark out tuberculous glands at the root of the lung. We get certain appearances even in healthy children which resemble very much infiltrations at the root, and although in a recent paper I showed certain pictures which are suggestive of infiltration of the gland at the root of the lung, I think we should hesitate as to their exact interpretation until we have autopsy material which will enlighten us as to the meaning of these appearances.

Dr. Isaac Adler: In our office, routine examinations with the fluoroscope are made on every patient, no matter what his complaint. Without going into the details of the methods pursued, it is only necessary to say that a very large screen covered with a lead glass plate is used. The screen is large enough to show at one glance the entire chest and very frequently also a part of the abdomen. By these means we have had exceptional opportunities for studying those shadows which Dr. Sewall mentions. Some of them are no doubt, as Dr. Sewall has said, dense vascularizations or even small consolidations, but not all of them are of this character. We know that especially at the hilus there are glands —bronchial, tracheal, mediastinal, of various shapes and positions, and that these glands are, as a rule, impermeable to the *x*-ray. They vary in size and distribution and are found almost without exception in every normal lung. It is only when they occupy peculiar positions away from the hilus; when they show by darkness of the shadow or by their size, inflammatory or degenerative changes, that we can connect them with tuberculosis. It seems certain to me from their position and from the lack of any pulsation that they are not connected with any of the large bloodvessels. In early cases of tuberculosis these shadows are usually increased on one side or the other of the median line or on both, and after some experience in practice it is not difficult to distinguish between the normal hilus shadow and the abnormal one. Not only in tuberculosis but also in lung tumors, mediastinal tumors, in leukemia, and in various other conditions are these abnormal shadows to be observed. If the clinical picture suggests the possibility of tuberculosis, and especially if we find by the fluoroscope characteristic changes in one or the other apex, these hilus shadows are more or less corroborative of the diagnosis. I would further say what Dr. Sewall has not mentioned, but which was mentioned a year or two ago by Dr. Lawrason Brown, that the heart itself in its peculiar shape and position, as shown by the orthodiascope, is often one of the earliest signs of tuberculosis.

STUDIES ON PNEUMOCOCCUS INFECTION IN ANIMALS

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In order to determine why it is that pneumococcus immunity is so strikingly manifest in the recovery of man from lobar pneumonia, and the action of immune sera on the pneumococcus so singularly deficient in the test-tube and in the treatment of infection, the following experimental studies were made on the action of dead pneumococcus material on animal tissues, action of immune sera on the pneumococcus, action of elevated temperatures on the pneumococcus, action of elevated body temperatures on pneumococcus infection, action of immune serum on pneumococcus infection, and finally, studies on the mechanism of recovery.

I present the more significant results of these studies, leaving details of the long series of experiments and discussion of them in full for more complete papers.[1]

1. ACTION OF DEAD PNEUMOCOCCUS CULTURES ON ANIMAL TISSUES

Intravenous, *subcutaneous*, and *intratracheal* inoculation of dead culture material failed to give rise to characteristic lesions. And yet, following the introduction of either culture filtrates or concentrated cultures containing masses of dead pneumococcus cells the animals became immune to the action of living virulent organisms. The immunity incited by the culture filtrates was proportionately greater than that incited by concentrated cultures, and intravenous inoculation was found to be more effective than subcutaneous.

Thus, this dead culture material did not contain the active poisons formed by the living organisms in infection.

[1] Journal of Experimental Medicine, 1912.

2. ACTION OF IMMUNE SERA ON THE PNEUMOCOCCUS

Agglutinative, precipitative, lytic, and opsonic action on the pneumococcus have been recognized in the blood serum of immunized animals. To the action of immune sera, however, the pneumococcus has proved singularly insusceptible.

Agglutination may be obtained in dilution by special methods, which I described in 1904 in a former paper.[1] With this improved technique I have since studied the reaction in pneumonia patients, and for purposes of control, in other diseases.

In health and in other diseases the agglutination rarely exceeded a dilution of 1 to 15. In 46 cases of pneumonia the agglutination varied from 1 to 20 to 1 to 300 and averaged 1 to 77. Owing to the fact that agglutination was often of low degree in both mild and severe cases, and failed to reveal significant fluctuations during or after the crisis, these reactions were of little practical value unless interpreted in the light of bedside observation.

Lysis of the pneumococcus in two of these sera from pneumonia patients was well marked in the lowest dilution; and in the sera of highly immunized animals I found the dissolution of the pneumococcus within its capsule described by Welch,[2] by Radiewsky,[3] and by Neufeld.[4] This lysis of the pneumococcus in immune sera often well marked, however, was invariably followed by growth of the surviving pneumococci.

Since the pneumococcus cell in culture undergoes early, marked, and often complete autolysis; since to the lytic action of bile the pneumococcus cell is exceptionally, almost specifically susceptible, and since bacteriolysis of pneumococcus cells in immune sera although evanescent may be readily seen in the hanging drop, it is evident that the lack of bactericidal action *in vitro* is not due so much to absence of lytic action in immune sera as to subtle qualities acquired by the pneumococcus through its parasitic adaptation.

The *opsonic* action of immune sera failed, in my experiments as in those of other observers, to bring about the phagocytosis of

[1] Journ. of Med. Research, 1904, vol. v, p. 228.
[2] Johns Hopkins Hosp. Bull., 1890, vol. i, p. 24.
[3] Zeitschr. f. Hyg., 1901, vol. xxxvii, p. 125.
[4] Ibid., 1902, vol. xl, p. 54.

virulent pneumococci. These, whether living or dead, were not taken up by the leukocytes *in vitro;* yet living non-virulent pneumococci were subject to the opsonic action of serum. This insusceptibility of virulent pneumococci may be attributed to the virulins of Rosenow[1] or the antiphagins of Tschistovitsch and Jurevitsch,[2] or simply to the presence of toxic substances.

In my experiments the pneumococcus cells suspended in salt solution and the culture fluid free from pneumococcus cells, when added to phagocytic mixtures of leukocytes and staphylococci, inhibited phagocytosis. This inhibition was neutralized by pneumococcus immune serum and to some extent by normal rabbit serum. These substances are thus in a degree specific and are in part set free from, and in part retained by, the pneumococcus cell.

Since both lysis and phagocytosis take place during recovery from infection the toxic and parasitic activities of the pneumococcus are inhibited or neutralized in some subtle manner in the tissues.

Inasmuch as the febrile reaction is one of the most striking features of pneumococcus infection in man, and this might be conceived as a conservative process, studies were made of the action of elevated temperatures on the pneumococcus in culture and then of the action of an elevated body temperature on pneumococcus infection.

3. ACTION OF ELEVATED TEMPERATURES ON THE PNEUMOCOCCUS

The thermal limits of pneumococcus growth as tested on 24 different strains in my experiments under the most favorable conditions for growth varied between 40.5° C. and 41.2° C., temperatures often attained or exceeded by the pneumonia patient. Above this, growth was not obtained with typical pneumococci; but streptococci grew at slightly higher temperatures. Just below this, growth often failed to develop when the conditions as to media, oxygen, and moisture were not the most favorable or in the least unfavorable. When first isolated from human infections the thermal limit of growth in media was 0.3° C. to 0.5° C. lower than later when strains

[1] Jour. of Infect. Dis., 1907, vol. iv, p. 285.
[2] Centralbl. f. Bakt., Ref., 1908, vol. xlii, p. 193.

had become fully adapted to artificial cultivation. At or just below the thermal limits of growth the integrity of the pneumococcus cell was most delicately balanced. The equilibrium was such that if growth failed to develop the bacterial cells were rapidly destroyed even in media favorable to growth when incubated a few tenths of a degree Centigrade lower. Thus the sensitiveness of the pneumococcus cell metabolism which is so well marked, even under the ordinary conditions of artificial cultivation, was greatly increased at the thermal limits of growth.

When virulent pneumococci in the sera of immunized animals were placed under the microscope or in the test-tubes, at temperatures above the thermal limit of growth, the destruction of the pneumococcus cells was often complete in three or four hours. The sera from normal animals and the exudates from disease processes possessed similar but less marked action.

In the light of these facts the conservative effect of the febrile reaction in infection is easily conjectured, but in order to secure definite experimental evidence of this the following studies were undertaken.

4. ACTION OF AN ELEVATED BODY TEMPERATURE ON PNEUMOCOCCUS INFECTION

Uninoculated and inoculated rabbits were placed in an incubator and the hyperthermy induced in each compared. The body temperature of the infected animals rose much more rapidly and was invariably higher until after excessive exposure when the mechanism of heat control was lost. During recovery, however, when infection was in a quiescent stage, the animals reacted more like the uninoculated animal. In severe infections when the animal was prostrated the development of hyperthermy during incubation was less and more difficult to induce than that of the uninoculated animal. Since the condition of hyperthermy brought about by incubation is chiefly if not wholly due to the prevention of heat loss, the relation of the action of the bacterial poison on tissue metabolism to the febrile reaction is apparent, and the condition of hyperthermy induced is, so to speak, a cumulative febrile reaction.

After inoculation the animal's temperature was easily raised by

incubation above 41° C. — the thermal limit of pneumococcus growth. To demonstrate the effect of this experimental hyperthermy on pneumococcus infection the experiments were conducted on unimmunized and partially immunized rabbits.

Experiments on the Unimmunized Rabbit. Unimmunized rabbits in sets of from 4 to 6 animals were inoculated intravenously with extremely virulent pneumococci. Two animals in each set were kept as controls the others were incubated at various stages of the infection. At no stage of these extremely virulent infections was it possible to demonstrate an inhibitory action from the hyperthermy. In only a few of the incubated animals was the infection prolonged and many died before the controls showing thereby that the animal was injured and infection favored. The results of blood cultures taken before and after incubation in these exceedingly virulent infections failed to show significant change.

Similar experiments with less virulent cultures, however, gave different results. In these the infection in incubated animals was often greatly prolonged, and from the blood cultures taken before and after incubation material reduction in the bacteriemia was often shown. But it was so difficult to secure these evenly balanced infections that the studies were continued with the partially immunized animal.

Experiments on the Partially Immunized Rabbit. Rabbits were inoculated with dead pneumococcus culture and after an interval of rest subjected to experimentation. The effect of incubation was more clearly shown in these animals. A crisis was often induced. Occasionally this proved to be a permanent cure, but often there was an evanescent return of the infection. Study of the blood by culture revealed marked reduction in the bacteriemia as a result of the incubation.

It was evident from these experiments that in the immunized as compared with unimmunized animal the action of the hyperthermy was clearly and uniformly apparent, and that as a result the effect of injury if present was masked. But the infection in these animals was uncertain. Some of the controls recovered and some of the incubated animals died. Studies with passive immunization were therefore made.

In these experiments the unimmunized rabbit after inoculation was incubated and treated with immune serum. The crises thus obtained in the incubated animals were more marked and complete as shown by the fall in temperature and the diminution or disappearance of the bacteriemia.

The incubation of infected animals thus resulted in considerable injury. This was due partly to the effect of the exposure and partly to the increased action of the poisonous material on the tissues. The development of the infection was thereby favored. But in the resistant animal this was offset by the inhibitory action of the hyperthermy on the pneumococci. Hyperthermy alone in the rabbit therefore failed to prove definitely conservative, but hyperthermy with experimental immunity was markedly so. In the tissues during infection the adjustment of these conditions of bacterial development and tissue reaction is nicely balanced and proportional in all its relations, a condition which can only be very crudely approximated in experimentation.

The febrile reaction includes not only elevation of temperature but the development of immunity as well; it is, in short, the reaction of the animal organism to the presence of the infectious material. Since in pneumonia the conditions of bacterial virulence and animal susceptibility[1] are evenly balanced, the conservative effect of the febrile reaction which proved so markedly on pneumococcus infection of animals under these conditions is evident. But in this immunity figures so prominently that the following studies were undertaken on the reaction of immune serum on pneumococcus infection and on the mechanism of recovery.

5. STUDIES ON THE ACTION OF IMMUNE SERUM ON PNEUMOCOCCUS INFECTION

The protective action of immune sera on pneumococcus infection of animals has long been recognized, but when immune sera have been used in the treatment of animals or man after infection has

[1] This is well shown by the development of extensive lung lesions in the partially immunized rabbit after tracheal injection and the absence of such lesions in the normal or predisposed animal. Experiments which were recorded in 1904, Amer. Jour. Med. Sci., cxxvii, p. 851.

become established the results have been less uniform and convincing.

I therefore made experimental tests of the action, first, of antitoxic sera obtained by immunization with culture filtrates[1] free from pneumococcus cells, second, of antibacterial sera obtained with washed dead pneumococcus cells, and, finally, of sera obtained with living virulent cultures.

Experiments with Antitoxic Sera and Experiments with Antibacterial Sera. Let it suffice to say of the results of these experiments that the curative value of both of these sera, obtained by immunization with dead culture material, was slight and of no practical significance. The antitoxic sera, however, often produced slight temporary improvement in the animal's condition, and this suggested testing this form of pneumococcus immunity in its active form.

In animals slightly immunized with culture filtrates free from pneumococci virulent inoculation gave rise to evanescent infection and was followed by a harmless parasitism during which the bacteriemia persisted, in one instance eight days, without signs of infection being manifest.

The presence of antitoxic pneumococcus immunity was thus clearly demonstrated. But this was not sufficiently exalted by immunization with this dead culture material to yield curative sera of practical value.

Experiments with Sera obtained by Immunization with Living Cultures. Rabbits were immunized with dead cultures; then intravenously with living cultures. Serum from these animals in experimental studies similar to those made with antitoxic and antibacterial sera was shown to possess marked curative action. When not administered too long after inoculation the animals were readily cured. For instance: Of ten rabbits inoculated intravenously with 0.05 c.c. of virulent culture, two were untreated, two were treated with normal rabbit serum, and six with immune serum. The serum treatment was given four hours after inoculation and twice the second day—in all three doses of 1 c.c. each. The untreated controls died in eighteen and twenty-one hours; those treated with

[1] These culture filtrates were obtained from twenty-four-hour broth cultures which were filtered through a Berkefeld filter. These filtrates were sterile as tested by subculture in broth.

normal serum in forty-eight hours; whereas of those treated with immune serum 4 recovered and 2 died, one the fifth, the other the seventh day after inoculation.

These sera also proved equally active on homologous and heterologous infection. But the action of this serum was largely antitoxic.

6. STUDIES ON THE MECHANISM OF RECOVERY

Following treatment with this serum crisis took place. The temperature at first rose and then fell sharply during the twenty-four hours following treatment. Blood cultures revealed marked reduction in the bacteriemia. In one of these experiments with excessive inoculations the bacteriemia of the controls, untreated and treated with normal serum, increased steadily and rapidly after inoculation, whereas that of the three animals treated with this immune sera fell in three hours from over 700,000 to 12 organisms per c.c., from over 8,000,000 to 106, from over 9,000,000 to 2500 in each instance. The leukocytes from the centrifugalized blood never contained pneumococci. This destruction of the pneumococcus was invariably extracellular but rarely, if ever, complete.

A few pneumococci survived. These gave rise to post-critical exacerbations which were evanescent and usually followed by a harmless parasitism without signs of infection. This harmless parasitism often lasted several days.

Signs of degeneration were found in the leukocytes. This was marked in all the controls and followed by destruction of the leukocytes. After treatment with this active serum these signs disappeared or failed to develop.

In these experimental crises the neutralization of the infectious material was therefore the dominant determining factor to which the destruction of the pneumococci present was secondary.

Pneumococcus infection of the dog was found to differ in many respects from that of the rabbit. These cannot be discussed in full. Let it suffice to say that marked bacteriemic infection or prolonged infection with sustained febrile reaction terminating in crisis were not found in the dog, but that in the lung of the dog typical lesions

were readily induced experimentally, and in these as in the circulating blood also phagocytosis took place.

By study on the dog infection similar to that made on the rabbit it was shown that in the blood and in the lung exudate after intravenous and intratracheal inoculation this phagocytosis varied. In the normal animal and in the immunized animal it was absent antemorten and after excessive inoculation. The destruction of the pneumococci which regularly followed inoculation was under these conditions chiefly if not wholly extracellular. But after more moderate inoculation phagocytosis was active even in the normal animal and greatly augmented in the immune animal and in the animal treated with immune sera. Phagocytosis in the dog thus varied with and was secondary to the neutralization of the pneumococcus poisons. The mechanism of recovery in the dog therefore did not differ fundamentally from that found in the rabbit.

Summary and Conclusions. It is evident from the results of these investigations that in culture the pneumococcus does not produce the active poisons it forms in infection, but that substances of a similar or a related nature are present. These are partly retained by the pneumococcus cell but largely and early set free in soluble form. Although these soluble substances give rise to an immunity which in its active form neutralizes the poisons developed in infection, this immunity is not sufficiently exalted to yield sera of definite curative value. By immunization with living cultures this immunity may be so exalted as to render the serum of marked curative value in infections of the rabbit.

It is further evident that despite the unsatisfactory results of the study of the reactions of pneumococcus immunity in the test tube, pneumococcus infection nevertheless conforms to the general law of infection offering one of the most striking examples.

As compared with diphtheria and tetanus organisms which each give rise to powerful poisons, but which possess little parasitic adaptation; the pneumococcus gives rise to poisons which are less active, or active only in the body tissues under conditions as yet little understood, but possesses marked parasitic adaptation.

In the tissues during infection pneumococcus poison is neutralized by the sera of immunized animals much as is that of diphtheria

organisms by antitoxin. In diphtheria the organisms are localized and the manifestations of the disease are largely if not wholly toxemic. Antitoxin neutralizes the toxemia and puts an end to the disease. In pneumococcus infection the organisms are rarely localized, but the manifestations of the disease are toxemic in that they are due to the action of the poison on the body tissues. The administration of the active immune serum obtained by immunization with living cultures, neutralizes the poisons of the infectious agents and puts an end to the manifestations of the disease rendering the parasitism of the pneumococcus harmless. These harmless parasites are then destroyed by lysis or by phagocytosis, or a few survive, giving rise to exacerbations when neutralization of their products ceases.

DISCUSSION

Dr. Rufus I. Cole: We have been much interested in the question of the serum treatment of pneumonia. A serum has been produced by the immunization of a horse, 0.2 c.c. of which will protect a mouse against 1 c.c. of a culture, of which 0.000001 c.c. will kill, that is against 10,000,000 lethal doses. It is evident that this is an extremely active serum. The curative effects of this serum, however, are slight, and this, as is well known, has been found to be true clinically of the sera previously prepared by others. Dr. Dochez has made certain investigations to determine, if possible, why it is that such immune sera are not efficacious when administered during the course of the disease. If 0.2 c.c. protects against 1 c.c. of culture, then 0.4 c.c. should theoretically protect against 2 c.c. of culture, etc. This is true, however, only to a limited extent, for he has found that as one increases the dose of culture, one has to use proportionately more and more serum, and a point is soon reached where the serum does not protect, no matter how much be given. This may be interpreted to mean that in addition to the immune bodies contained in the serum, something must also be supplied by the body, and this substance is, under ordinary circumstances, supplied only to a limited extent. Sufficient immune bodies can readily be supplied, but the body cannot prepare a sufficient amount of the complementing substance, whatever this complementing substance may be. We feel that the failure of the body to produce this substance is the reason why these sera are not effective when there is a pronounced infection present. It would seem that in the future our efforts must be directed toward the discovery of methods for inducing the body to produce this complementing substance in increased amounts.

Dr. M. J. Rosenau: What evidence has Dr. Wadsworth that in pneumonia there is a free or toxic substance that may be neutralized by this antiserum that he experimented with?

Dr. Wadsworth: In regard to Dr. Coles' experiments, of course the conditions are not comparable. In my experiments the tests were made with the curative action of serum administered several hours after inoculation. In some instances in order to study the conditions present excessive doses were given. In one experiment 5 c.c. of virulent culture were introduced in order to secure exaggerated conditions of bacteriemia and to determine the changes in the bacteria during the crisis induced. In such instances twice as much serum as culture was used. Minute doses of culture were never used in the tests. Ordinarily the doses were from 1 c.c. to $\frac{1}{4}$ or $\frac{1}{10}$ c.c. for the original inoculation of these very virulent cultures. The difference between curative and protective action of sera is important. It is one thing to give serum before or with the virulent culture inoculated and it is quite another thing to give serum after inoculation when infection has become established.

In regard to Dr. Meltzer's point about the possibility of hypersusceptibility accounting for the recurrence of pneumonia I think recurrence is quite as reasonably explained by the ordinary fluctuations in resistance, and this is supported by the fact that the extent of lung lesion is simply an expression of the resistance of the individual. If a susceptible animal is injected through the trachea with virulent cultures of the pneumococcus there is little or no lung lesion, but if a susceptible animal is partially immunized and inoculated through the trachea the lung reactions are more marked.

In reply to Dr. Rosenau's question about the solubility of these substances, I did not realize that the substances giving rise to the immunity were soluble when I began my work on dead cultures. But I used filtrates which were obtained from pneumococcus growths at the end of twenty-four hours, and passed through a Berkefeld filter so that no organisms were present. The maximum effect of one immunizing dose of these culture filtrates was much more than with corresponding qualities of pneumococcus cells. Although this immunity could not be exalted with the filtrates to give an antitoxic serum which was effective curatively, it could be demonstrated in its active form in the animal. Infection developed as a harmless parasitism in these animals immunized with filtrates, and this harmless parasitism was quite comparable to the harmless parasitism which followed treatment with the active serum obtained from animals immunized with living virulent cultures.

INFECTIONS FOLLOWING TONSILLOTOMY WITH A CONSIDERATION OF THE FORMS OF SUCH INFECTIONS

By HENRY KOPLIK, M.D.
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During the last twenty-five years our knowledge of infections with the tonsil as a port of entry has been enlightened to a considerable extent, both from an experimental and clinical point of view. The evidence that such infection takes place is overwhelming. Speaking of nurslings and children, Gundobin asserts that the tonsils have a pathological significance due to, on the one hand, their hyperplasia, and on the other hand, their capability of transmitting certain infections. We meet hyperplasia of the tonsillar tissue not alone most frequently from the fourth to the eighth year of life, but in the newborn and the adult. The tonsils, the pharynx, and nasopharynx with its adenoid tissue, the peritonsillar tissue and the lymph nodes and lymphatic tissue of the retropharynx form one connecting ring by which infections may pass from the tonsil into the general circulation. I will not discuss the question as to whether the tonsil must be traumatized in order that infections may penetrate into the deeper structures. This seems to me a question of rather academic interest in face of the clinical facts that infections traceable to the tonsils may be closely connected with the appearance in quick sequence of rheumatism, endocarditis, pneumonia, nephritis, orchitis, appendicitis, etc. The literature, which is quite extensive, is not lacking in furnishing evidences of infections as hinted above. Moreover, forms of so-called cryptogenetic infections are traced to old tonsillar foci. Gwosdinsky reports such a case the principal symptoms of which were numerous

large hemorrhages into the skin with staphylococci circulating in the blood and suppurations of various organs, traceable to an old retropharyngeal abscess. Tischutkin publishes a fatal case of bacterial sepsis as a result of tonsillar infections and emphasizes the importance of the tonsils as a source of cryptogenetic infection. Baup injected the tonsils with tubercle bacilli and showed that these could pass to the lymph passages of the neck and mediastinal lymph nodes. Grober did much the same work with carmine. Menzner investigated the peritonsillar tissue in cases of rheumatism, and concluded that by this route bacteria obtained access to the blood current, causing endocarditis and rheumatic manifestations, under certain conditions the normal protective arrangement of the lymphatic pharyngeal ring is overcome and bacteria pass in a virulent state into the circulation. It is not yet clear why these things occur in certain individuals and not in others. It seems to me that much more is needed than a simple infection of the tonsils to presuppose a systemic infection. We all have seen patients repeatedly attacked with tonsillar infection and yet no systemic invasion resulting in choreal, endocarditic or rehumatic manifestations occurred. We must, rather, assume some systemic individual idiosyncracy which allows of such a result, else the simple fact of the presence of a tonsillitis would be universally disastrous.

Years ago, Packard showed, from a purely clinical standpoint, the sequence of endocarditis and tonsillar infection; and, later, Forcheimer cited instances of systemic infections including appendicitis and infectious jaundice as a sequence of tonsillitis. The appearance of an endocarditis in the course of a tonsillar infection is certainly, today, not a novel experience, on the other hand general severe septicemia following catarrhal angina is a matter of record (Tollens). Such cases are exceptional, but they do occur. An angina may result in simple swelling, redness of the fauces (bacteriemia), or in severe inflammation of the lymph nodes, secondary suppurations (appendicitis), osteomyelitis, endocarditis, and signs of sepsis of the internal organs without bacteriemia, or there may be angina with endocarditis, acute nephritis, cholecystitis, encephalitis, arthritis, where changes grossly clinical in the neck are slight (Kretz), and there is no bacteriemia.

Lingelsheim found streptococci constant in and on the tonsils in the normal pharynx and nose, and this fact is frequently confirmed in the literature. The least irritation increases in numbers these normal habitants of the tissues. It is only additional evidence to quote the literature to any greater extent to prove our thesis that the tonsils play a role in systemic infections which daily experimental pathological and clinical data go to confirm. The whole mass of literature may be summed up to show that tonsillar infections may first cause simple febrile disturbances without septicemia; they may result in systemic infections causing endocarditic, rheumatic joint, and choreal manifestations, and finally, as in the case of Gwosdinsky, septicemia with hemorrhagic manifestations and fatal issue.

If the tonsil *in situ* is such a source of danger as a port of entry of infections the organ, when the subject of traumatism or operation, opens up a whole area which easily takes up infection. In recent years it has been my observation that, after tonsillotomy or enucleation of the tonsils, with or without the removal of the adenoid growths in the nasopharyngeal space, certain forms of infection are apt to arise. It is surprising that those whose work lies in this special field of surgery are not impressed with this danger. The nose and throat surgeons, as a rule, do not see all of their cases after operation, and inquiry among them elicits very little data as to the infections which are the theme of this paper. In fact, in one case a surgeon asserted that he had performed a thousand or more operations on the tonsils and adenoids without once having observed a case of infectious fever following the operation. Inasmuch as the statement was made in a conference, and the case on which he had operated was running a septic temperature subsequent to the operation, it may be seen that these cases have not as yet received the full attention they call for.

There are three forms of infection which I have seen following the removal of the tonsils or adenoids, or both.

1. After an operation the patient may appear to be doing well, but on the second or third day begins to run a temperature of varying severity. A careful examination of the chest and throat fails to reveal any cause for this temperature, and in the cases which I

have in mind the heart remains normal and there is no development of a murmur or any signs of endocarditis. The lymph nodes in the neck may not be enlarged, the patient recovers after a week or more, and no sign of any other lesion is found to account for the run of temperature.

In the cases I refer to the ears are blameless, and here I will exclude from any consideration those numerous cases in which, after operation, the ears became the seat of inflammation by apparent extension of inflammatory processes of repair, or inflammatory exacerbation from the pharynx.

Not long ago I was called to see a case of a boy aged about nine years. He was quite well before his tonsillectomy; the physician had advised ablation of the tonsils as a hygienic measure. The operation was neatly and successfully accomplished. After twenty-four hours the patient began to run a high temperature, 103° to 104°. On examination the physical condition of the patient showed absolutely nothing. When I saw the patient the necrotic areas generally seen after operation had fully cleared off and the throat looked clean. The patient ran an obscure temperature for two weeks and then recovered without ill effects on the heart and no rheumatic manifestations. Since seeing this case I have heard of and seen similar cases, but inasmuch as I have not been allowed to examine the cases myself I cannot vouch as to the absence of other lesions, as in the typical case related. I have the conviction that such cases are not uncommon.

2. A second set of cases are those in which, after ablation or enucleation of the tonsil, the patients run a moderately high temperature for weeks and develop cardiac murmurs, or even in a short time after operation develop the signs and symptoms of a malignant form of septic endocarditis, and die. Of this latter form of infection it can be said that they must be extremely rare, but they certainly do occur.

The following is a very instructive example of such an infection which I published some years ago.

A boy, aged ten years, suffering from manifestations of rheumatism in the form of a mitral regurgitant murmur of old standing had a mild form of chorea. While the chorea was in progress the patient

being up and about, he was operated upon and the tonsils and adenoids were removed. Three days after the operation the patient was seized with a chill and fever, and an exacerbation of the chorea. Examination of the heart at this time showed a periendocarditis. In the second week he became delirious, complained of precordial pain, and ran a high febrile curve. He developed, also, petechiæ, and died after an illness of two weeks. This case was seen by others in consultation and the opinion was unanimous that the operation had precipitated the violent form of sepsis from which the patient succumbed.

A much milder form of sepsis, but just as disquieting, occurred in a case of a child, aged seven years. She was in perfect health. Her tonsils were not large, but the surgeon said they were the seat of erosions, and advised removal in spite of the perfect condition of the child. The tonsillar tissue, which was successfully removed by enucleation, was not great in bulk. The child apparently weathered the operation successfully. Three days after the operation it was noticed that the child was not herself, and investigation revealed a temperature running quite high. After some days of illness I saw the case. She had been running an irregularly remitting curve of temperature. Her fever would mount as high as 104° to 105°, and fall to almost normal. Under antipyretics the temperature would stay at or near normal for one or two days, and then mount again. The throat at the time I saw the patient had cleared of all necrotic tissue. The patient had a flushed appearance, and after a week of fever had lost ground physically, otherwise she was in good spirits. There was a slight bruit over the apex and base systolic in time, and on one conjunctiva there was a doubtful petechial spot. A blood culture failed to reveal bacteria, but the course was that of a mild endocardial infection, lasting over three weeks, with recovery. This case was seen, also, by others and the opinion of a postoperative infection appeared to be conclusive. All other forms or causes of infection, such as typhoid, or even mild chest infections, or paratyphoid infections, were excluded and not entertained. The sequence of the febrile attack so immediate upon operation, the absolute exclusion of everything pointing to other organs, left only the one conclusion of a postoperative infection.

3. The third form of septic infection following tonsillotomy or adenectomy, which I have seen, resembles more a hematogenous borne infection and is of interest in view of the case cited in the first part of this paper by Gwosdinsky, in which the sepsis took the form of extensive hemorrhages throughout the body.

Female, aged five years, admitted to the service January 17, 1912. Discharged February 27, 1912.

Family History. Negative, no hemophilia.

Past History. Measles at two years, varicella at four years, never bled profusely, always a mouth breather. Three weeks before admission her tonsils and adenoids were removed at an institution devoted to the treatment of diseases of the nose and throat.

Present History. Since the day following the operation the child has been running a temperature of 104° to 105°. Two weeks before admission she began to cough, with mucoid expectoration, but on examination no distinct pneumonia could be established. Three days before admission to the hospital patient began to bleed from the lips. Ecchymosis appeared on the skin of the back, and two days before admission the patient bled profusely from the rectum. This intestinal hemorrhage was repeated several times, and for this she was transferred to the hospital. There were no chills, no sweats.

On Admission. The patient was fairly well nourished, but anemic. There were several large ecchymotic areas on the back, buttocks, and thighs, and petechiæ over the upper and lower extremities. The rectum was filled with blood clots. There was bleeding from fissures in the lips. The conjunctivæ showed petechiæ. The cavities where the tonsils were located were raw surfaced and blue; there was blood in both nostrils. The postcervical and submaxillary glands were palpable. The lungs showed a dull area over the left side, behind, with a few crepitant rales, otherwise negative. The heart a slight systolic blow at apex.

On Admission. Blood: Red blood cells, 3,744,000; white blood cells, 22,000; polynuclear leukocytes, 72 per cent.; lymphocytes, 25 per cent.; eosinophiles, 3 per cent.

Subsequent to Admission. The patient ran a febrile course and more petechiæ developed over the surface, and one or two hemorrhages occurred from the bowel.

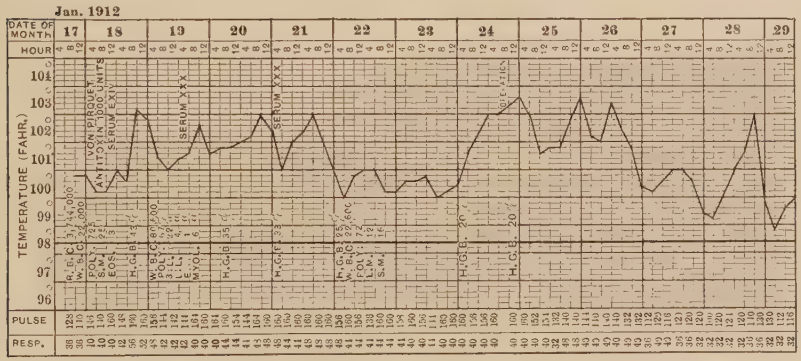
Heart murmur became more pronounced and was heard over the whole precordium and at the apex. The pallor increased, the hemoglobin steadily diminishing to 25 per cent.

January 24. The anemia increasing in face of the fact that no new petechiæ appeared and no additional hemorrhages from the bowel occurred after the injection of 75 c.c. of human blood serum the first

three days after admission. January 24 the hemoglobin sank to 20 per cent., this in face of the fever and sinking condition of the patient, a direct blood transfusion was performed, the father being donor, by Dr. A. Moscowitz, of Dr. A. Gerster's service. Hemoglobin rose to 65 per cent.; wound healed by primary union.

The subsequent history was one of uninterrupted convalescence, the lung signs persisting for some time.

On discharge of the patient blood examination showed: Red blood cells, 5,560,000; white blood cells, 12,800; hemoglobin, 88 per cent. Differential: Polynuclears, 38 per cent.; lymphocytes, 61 per cent.; eosinophiles, 1 per cent. A blood culture taken before the transfusion and during the course of the temperature failed to show bacteria.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to 20 per cent. The patient also developed more marked signs after admission of a bronchopneumonic process over the lower lobe of the left lung behind. She was still running a temperature of 103° and sinking when I determined to have a direct transfusion performed. This was done, the father being donor. After the transfusion the temperature gradually sank to the normal and from this time the patient remained convalescent, and was discharged in a normal condition both as to her blood and physical state. The murmur which was present on admission disappeared after transfusion completely, proving conclusively its hemic origin. The culture of the blood taken in the course of the illness was negative for bacteria, and, on account of the extremely critical condition of the patient, was not repeated.

Here is a case of true hematogenous sepsis following tonsillotomy and adenectomy in an institution, performed under the most excellent hygienic conditions. There was, in this case, no history of hemophilia, or any bleeding tendencies in the family or the child. The case resembles very much those cases which we meet from time to time in which leukemic blood conditions seem to have followed some operation on the tonsils, and instances of which are cited in the literature. The case is unique, inasmuch as the transfusion was performed for a progressive anemia which continued after the hemorrhages on the skin and from the intestine had ceased, and which recovered in the face of an evident sepsis in progress at the time of transfusion. The transfusion was performed as a last resort, to save the life of the patient.

In this paper I have called attention to three distinct forms of sepsis which followed upon surgical removal of the tonsils:

1. The form which runs an obscure fever for a week or more without causing any endocarditic or other lesions.

2. Those cases which run a temperature and combine with them the manifestations either of a mild infectious endocarditis, or in which, as in the case of chorea, the endocarditis takes on a severe infectious (or, as it is called, malignant) type, with subsequent fatal issue.

3. A third form of sepsis is that in which the infection is evidently severely hematogenous and causes destructive blood changes, with

signs of sepsis such as profuse hemorrhagic ecchymotic areas on the surface of the skin, petechiæ, severe hemorrhages from the bowel, and areas of obscure bronchopneumonia.

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DISCUSSION

Dr. James Tyson: I have recently had under my observation in consultation one case which perhaps more nearly approaches the second category which Dr. Koplik has given us. An adult three days after the removal of tonsils was seized with chill and fever and continued in this state with varying temperature, but without any definite signs of local lesion. At my first visit I found what seemed a condition of sepsis with very sharp pleuritic pains, associated with a moderate degree of impaired resonance which I though might have been an embolic pneumonia. At the end of the week I saw him again. During that time there had been an intermission of the fever and then recurrence. The man was evidently worse and I discovered in the opposite part of the chest a few friction rales which I ascribed to pleurisy, and after that a steady progression from bad to worse until the man died in profound sepsis. If we place the pleura in the position of the endocardium this case might perhaps fall into the second class rather than the first.

Dr. E. Libman: I have seen one case belonging in the first group described by Dr. Koplik. I would like to inquire whether he has found any change in the lymphocyte count; in my case it was increased.

Dr. S. J. Meltzer: I don't suppose that Dr. Koplik means that these three diseases followed because tonsillectomies were done. Is it not possible that in these cases an early stage or a mild form of infection prevailed before the tonsillectomy was performed, and that the latter aggravated the course of the disease?

Dr. John W. Brannan: I should like to ask Dr. Koplik in what proportion of cases does this infection occur? In all the cities a large number of these operations are performed practically every day. The school teachers and school nurses bring the children to the hospitals for operation. In the four hospitals I am connected with there must be twenty or thirty such operations in each hospital during the week, and I have yet to hear of such a condition as this.

Dr. Koplik: Dr. Meltzer asked whether I thought that these conditions followed as the result of the tonsillectomy. I certainly do. I bring that out in my paper. The literature shows that such a thing is possible experimentally. Bacteria exist about the neck and tonsillar ring and these bacteria are called into play by the operation—not criticising the interference at all in any way. These infections must be quite frequent. There was leukocytosis before the transfusion in the septic hemorrhagic case.

METABOLISM IN DIABETES

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Two years ago Dr. Benedict and I reported a series of metabolism experiments upon diabetic patients, as a result of which we were able to show that the metabolism in diabetes was 15 to 20 per cent. above that of health. The result was so unexpected that it awakened criticism of the work chiefly in regard to the number of our control cases and to the difference in their weight as compared with diabetic cases. It is, therefore, a pleasure to report today that we have been able to greatly increase our number of normal as well as diabetic cases, and also have met the second part of the criticism by securing a normal individual of equivalent size and weight for each diabetic patient. The second group of cases has confirmed our original contention that the metabolism was increased. The following table gives the results of the work reported two years ago together with the old and the recent work combined. The oxygen alone is given for the combined work as that is the factor of chief significance. It will be seen that whereas the increase in metabolism as measured by the oxygen consumption was 16.5 per cent. over the normal in the first series, the increase reached 22.4 per cent. in the combined old and recent experiments.

In 18 cases of severe diabetes studied, the metabolism was compared with normals of equivalent height and weight, and in each case the diabetics showed increased metabolism.

During the first study the data obtained suggested that the severer the diabetes the higher the metabolism. We have followed

up this point and now feel warranted in reporting this as a fact. This is shown in two ways: first, by a comparison of the diabetic cases arranged in groups as mild and severe, and secondly, by the increase in metabolism in individual cases as the disease has progressed in severity as determined by the carbohydrate balance and the acidosis. Unfortunately our number of mild cases is smaller than we would wish, but the evidence appears sufficient to warrant the conclusions that the metabolism increases with the severity of the disease.

DIABETICS VS. NORMAL INDIVIDUALS PER KILOGRAM OF BODY WEIGHT

Total cases.	Total number of experiments.	Subjects.	Carbon dioxide per minute.		Oxygen per minute.		Heat per twenty-four hours.	
		First series of experiments.	Chair. c.c.	Bed. c.c.	Chair. c.c.	Bed. c.c.	Chair. Cals.	Bed. Cals.
10	52	Normal	3.26	3.05	3.99	3.63	29.0	24.2
10	33	Severe diabetes	3.53	3.21	4.85	4.23	33.6	27.6
		Percentage increase over normal	8.3	5.2	21.6	16.5	15.9	14.0
		Combined old and new series of experiments.						
25	272	Normal	....	....	....	3.71		
18	61	Severe diabetes	....	....	....	4.54		
		Percentage increase over normal	....	....	....	22.4		

In conclusion, we should like to call attention to what appears as the key to the solution of the cause of this increased metabolism. In an experiment upon himself for another purpose, Mr. Higgins, of the Nutrition Laboratory was thoughtful enough to determine his metabolism while living upon a carbohydrate-free diet. He found that his metabolism was distinctly increased above his normal metabolism. Coincidently an acidosis of moderate degree appeared. We repeated this experiment and also obtained an increase in the metabolism of the individual. The obvious inference, therefore, is that the increase in the metabolism of diabetes is due to the withdrawal of the carbohydrates from the diet and quite probably is directly due to the resulting acidosis.

NORMAL INDIVIDUALS ON CARBOHYDRATE-FREE DIET

Subject.	Date.	Day of diet.	Oxygen absorbed per minute. c.c.	Respiratory quotient.
H. L. H.	1911	Preliminary	237	0.84
	September 7	2d	299	0.67
	September 8	3d	280	0.71
	September 9	4th	272	0.72
H. H. A.	December 27	Preliminary	224	0.90
	December 28	1st	258	0.74
	December 29	2d	258	0.70
	December 30	3d	236	0.74
	December 31	4th	242	0.71
	1912			
	January 1	5th	239	0.69

Many interesting subjects for discussion and experiment are thus raised and we hope to be able to still further extend our investigations in this direction.

The first series of experiments were published in a monograph of 234 pages by the Carnegie Institution of Washington. Publication No. 136, under the title of "Metabolism in Diabetes Mellitus." The second series will be published in the same series of publications under the title, "A Study of Metabolism in Severe Diabetes."

DISCUSSION

DR. A. E. TAYLOR: I should like to report in connection with Dr. Joslin's work, some results of Dr. Ringer that can be obtained by the injection of sugar into the fully phloridzinized dog. Let us say that a dog weighing a certain number of kilos has a metabolism output of 10 grams N per day. If that dog be given a very large dose of sugar the metabolism will fall 50 to 70 per cent. Despite that fact the sugar is not burned. We will recover the sugar in twenty-four or thirty-six hours. So soon as the sugar is eliminated the metabolism rebounds to its original high figure.

DR. JOSLIN: I think the supposition that Dr. Taylor has put forth is very likely correct, and I think he will find a confirmation of it when our experiments are published. Just how the carbohydrate acts probably neither Dr. Taylor nor Dr. Benedict would care to explain. We have noticed many quite analogous examples to this in our work with diabetic patients. I feel that we owe a great deal to Dr. Taylor in raising, two years ago, various criticisms upon our work, and it shows the advantage of discussion of papers to the men who read them.

ON ACTION OF DIGITALIS AND DIGITALIS-LIKE SUBSTANCES ON THE RIGHT VENTRICLE

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OF NEW YORK

(From the Department of Physiology and Pharmacology of the Rockefeller Institute)

The literature upon digitalis and digitalis-like compounds is enormous in its extent, and an apology is almost necessary for adding to it. In extenuation, however, I may mention that the facts to be reported have not been described as far I am aware.

When rabbits receive, peritoneally or intravenously, an injection of any of the ordinary digitalis preparations or of strophanthin (Thoms), so that death is caused often within one-quarter of an hour, an immediate autopsy shows, as a rule, that the heart is perfectly quiescent; there is no beat visible either in the large veins, auricles, or ventricles. The heart is moderately dilated and does not respond to mechanical or electrical stimulation as Stannius[1] first showed in cats. If such a heart is now excised and slit open, the endocardial surfaces of the two ventricles show an interesting and perhaps important difference. The columnæ carneæ of the right ventricle, especially the muscle trabeculæ near the auriculoventricular junction, look more grayish than normal, and when scraped by the finger-nail show a marked degree of toughness which may even approximate that of connective tissue. The left ventricular muscle, on the other hand, does not resist the finger-nail, which easily scoops up some of the tissue, except on the bases of the papillary muscles. This toughening

[1] Arch. f. physiolog. Heilk., 1851, x, 199. Curiously enough, Stannius could not obtain this result in rabbits.

of the muscle tissue is not equally pronounced over the entire right ventricle; the lower third seems to be practically as soft and non-resistant as normally. When the hearts of normal rabbits are examined no such striking difference between the two ventricles can be observed, though sometimes the right ventricle seemed to be perhaps a trifle firmer than the left when tested. Microscopic examination of these digitalis hearts has so far shown no marked structural change in the right ventricle which would differentiate it from the left.

As far as I know, this change has not been described by anyone. Numerous observers have, of course, seen the state of tonic ventricular contraction which is so characteristic for the action of digitalis compounds on the frog's heart, but in the rabbit the heart muscle is, as a rule, fairly relaxed, and all the chambers filled with blood when the autopsy is made at once after cardiac stoppage. I have observed a similar change in the right ventricle of rabbits which died acutely of serum anaphylaxis.[1] As the blood-pressure picture in this type of anaphylaxis is very similar to that produced by lethal doses of digitalis preparations, and as the heart changes macroscopically are very similar to those obtained after the employment of digitalis compounds, I feel justified in considering the lethal cardiac action of serum anaphylaxis in the rabbit a digitalis-like action. This similarity of attack explains adequately why anaphylactic rabbits died more quickly after the injection of digitalis preparations than those which did not receive any.[2]

Interpretation of Results. It will be observed that the muscular cardiac changes briefly described above are located in areas which form a part of the conducting system of the heart. A marked gross anatomical change such as that described ought surely to have an effect upon the coördination of the heart beat at a time when this change is not yet so pronounced as to cause cardiac stoppage and death. This is indeed true both for digitalis as well as for cardiac anaphylaxis in the rabbit. It is well-known that digitalis may not only abolish some cardiac irregularities, but that they also can be produced by an injudicious exhibition of this drug,

[1] Auer, Journal of Exp. Med., 1911, xiv, 486.
[2] Auer, loc. cit., p. 490.

and there are numerous investigations which have dealt with this fact. In lethal cardiac anaphylaxis of the rabbit I have directly observed the production of a partial heart block and a graphic record may be found in a section of the curve reproduced in Plate I[1] where the auricles beat three or four times to one ventricular contraction. In these cases, however, it might be argued that anaphylaxis produced this change only in lethal cases. But there are other graphic records from rabbits which did not die or succumbed only after an hour or two, which demonstrate a similar condition. In these experiments the volume changes of the thoracic cavity as well as the carotid blood pressure (Hürthle) was recorded. The volume tracing of the thoracic cavity recorded also the volume changes of the heart, and on this curve, especially during expiratory pauses, the heart record came out with great purity. On such tracings it was found that the volume heart record showed three and four times as many beats as were recorded by the Hürthle membrane manometer. Some other structure, probably the auricles, were therefore beating two and three times as fast as the heart, for the ventricular beat was, of course, also registered on the volume tracing. These variations were transitory; the three to one rhythm occurred four minutes after the injection of the toxic dose of horse serum and lasted a few minutes when a two to one rhythm set in; fifteen minutes later the tracings showed a one-to-one rhythm and a normal blood pressure.

It is therefore seen that cardiac anaphylaxis in rabbits is again similar to the effect produced by digitalis compounds.

Summary. Digitalis and digitalis-like substances in lethal doses produce a marked change in the right ventricle of rabbits, which is only slightly indicated in the left ventricle.

The entire heart is fairly relaxed at first and does not respond to mechanical or electrical stimuli.

The columnæ carneæ, especially the muscle trabeculæ of the right ventricle, show a marked toughening and resistance to the finger-nail. This resistance is only slightly indicated in the left ventricle, and there only at the bases of the papillary muscles.

[1] Auer, loc. cit., Plate I.

Similar changes are produced in cardiac serum anaphylaxis in rabbits. Evidence is advanced that these cardiac changes in serum anaphylaxis cause marked transitory disturbance in the coördination of the heart beat.

Compounds of the digitalis group should not be used therapeutically in cases of cardiac serum anaphylaxis, as both produce similar lesions of the heart muscle.

CERTAIN CLINICAL FEATURES OF SUDDEN OBSTRUCTION OF THE CORONARY ARTERIES

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Obstruction of a coronary artery or of any of its large branches has long been regarded as a serious accident. Several events contributed toward the prevalence of the view that this condition was almost always suddenly fatal. Parry's writings on angina pectoris and its relation to coronary disease, Jenner's observations on the same condition centring about John Hunter's case, Thorvaldsen's tragic death in the theatre in Copenhagen with the finding of a plugged coronary, sharply attracted attention to the relation between the coronary and sudden death. In Germany Cohnheim supported the views of Hyrtl and Henle as to lack of considerable anastomosis, and as late as 1881 lent the influence of his name to the doctrine that the coronary arteries were end arteries; his Leipzig necropsy experience, as well as experiments on dogs, forced him to conclude that the sudden occlusion of one of these vessels or of one of the larger branches, such as the ramus descendens of the left coronary, meant death within a few minutes. Others emphasized the same view.

No one at all familiar with the clinical, pathological, or experimental features of cardiac disease can question the importance of the coronaries. The influence of sclerosis of these vessels in the way of producing anemic necrosis and fibrosis of the myocardium, with such possible results as aneurysm, rupture or dilatation of the heart is well known. So also is the relation of the coronaries to many cases of angina pectoris, and to cardiac disturbances rather indefinitely classed as chronic myocarditis, cardiac irregu-

larities, etc. It must be admitted, also, that the reputation of the descending branch of the left coronary as the artery of sudden death is not undeserved.

But there are reasons for believing that even large branches of the coronary arteries may be occluded, at times acutely occluded, without resulting death, at least without death in the immediate future. Even the main trunk may at times be obstructed and the patient live. It is the object of this paper to present a few facts along this line, and particularly to describe some of the clinical manifestations of sudden yet not immediately fatal cases of coronary obstruction.

Before presenting the clinical features of coronary obstruction, it may be well to consider certain facts that go to prove that sudden obstruction is not necessarily fatal. Such proof is afforded by a study of the anatomy of the normal as well as of the diseased heart, by animal experiment, and by bedside experience.

The coronaries are not so strictly end arteries, *i. e.*, with merely capillary anastomoses, as Cohnheim and others thought. By careful dissections, by injection of one artery from another, by skiagraphs of injected arteries, and by direct inspection of hearts made translucent by special methods, there is proof of an anatomical anastomosis that is by no means negligible.

Jamin and Merkel's[1] beautiful stereoscopic skiagrams show the remarkably rich blood supply of the heart with occasional anastomoses between vessels of considerable size. The possibility of injection of one coronary artery from the other is admitted even by those who deny that such injection proves more than a capillary non-functioning anastomosis. Amenomiya,[2] by injecting hearts of young persons, showed naked-eye anastomoses in subepicardial tissue. He feels that Hirsch and Spalteholz have nearly cleared up the question as to the relation between the heart muscle and disease of the coronary artery from the anatomical standpoint.

[1] Die Koronararterien des Menschlichen Herzens in Stereoskopischen Röntgenbildern, Jena, 1907 Extensive bibliographies are contained in the articles by Thorel, Lubarsch-Ostertag's Ergebnisse, ix, Abt. 1, and in Amenomiya, Virch. Arch., Band cxcix, 1910. I repeat only some of the more important references and add new ones.

[2] Ueber die Beziehungen zwischen Koronararterien und Papillarmuskeln im Herzen, Virch. Arch., Band cxcix, S. 187-214. Hirsch und Spalteholz, Coronararterien und Herzmuskel, Deutsch. med. Woch., No. 20, 1907.

Hirsch says that in dogs the anastomosing vessels are functionally competent, and Spalteholz says that in man the vessels are nearly the same as in dogs, rich in anastomoses even in those of considerable caliber. The latter investigator, by a method of injection and treatment of the heart so as to make the muscle transparent, shows to the naked eye that there are anastomoses of considerable size. Among others who are on record as believing there are non-negligible anastomoses may be mentioned Haller, Huchard, Orth, Michaelis, Langer, Legg, and West. All recognize, however, that there are individual differences, and also that though the heart may show rich anastomoses, these are not necessarily functional, *i. e.*, that an artery that anatomically is not a terminal artery may yet be such functionally.

But there is proof not only of anatomical connection between the two coronaries, but that in certain instances, at least, such connection is of functional value. Experiments on lower animals and the clinical experiment of disease of the coronaries with autopsy findings show this.

Much of the earlier experimental work on the lower animals, obstructing the coronary arteries by ligatures, clamps, or artificial emboli, gave a promptly fatal result. Among those who worked along this line and reached these conclusions may be mentioned Erichsen (1842), Panum (1862), von Bezold, Samuelson (1880), Cohnheim and Schulthess-Rechberg (1881), G. See, Rochefontaine and Roussy (1881), Bettelheim (1892), Kronecker, and, to some extent, Michaelis. The work of Cohnheim[1] attracted particular attention, and his conclusions as to end arteries, irreparable injury, and cessation of the beat of both sides of the heart within two minutes from the time of shutting off the coronary circulation confirmed and elaborated the conclusions of the earlier experimenters, and was in turn confirmed by the French writers just named, by Bettelheim, and others.

But soon dissent was heard from various quarters as to many of Cohnheim's results, and among other things as to the sudden death following the ligations. Michaelis found that the injury

[1] Ueber die Folgen der Kranzarterlenverschliessung für das Herz, Virch. Arch., lxxxv, 503.

from ligation in rabbits was not so serious or irreparable as in dogs. Fenoglio and Drouguell, in 1888, found that some dogs might live. Porter showed that after ligating one or two large branches of the coronary artery a dog might live hours or days. More than half his animals lived after ligating the descending branch of the left coronary. Von Frey, at the Congress for Internal Medicine in 1891, doubted the sudden stopping of the heart as Cohnheim taught; said that clearly the greater weight should attach to those observations in which the ligation was borne without harm, and that the stopping of the heart is not a *necessary* consequence of the obstruction of a large coronary branch. Hirsch in 8 dogs and 2 apes had no sudden deaths from ligation. Bickel,[1] under Orth and Amenomiya, had a dog live nineteen days, and killed two dogs, one on the eighth and the other on the seventeenth day after ligating the descending branch of the left coronary. Kolster ligated smaller branches; his dogs lived, and when killed at intervals of several weeks showed the progressive changes of fibrosis of the myocardium. Imperfect technique, by which damage was done to the heart muscle and pneumothorax produced, is offered as a partial explanation, at least, for the more rapidly fatal results obtained by Cohnheim and others. Miller and Matthews[2] call attention to the better results where ether is employed as an anesthetic rather than curare or other drug. With ether they were able to ligate larger branches, many of their dogs living several days.

Experimentally, then, sudden death, even late death, is not a necessary consequence of obstruction of even large branches, such as the descending branch of a coronary artery.

There are numerous autopsy observations, frequently with helpful clinical history, that show directly or by inference the existence of efficient anastomoses, and the ability of the heart at times to survive the obstruction of a coronary or some large branch. Some of these instructive cases may be mentioned. Pagenstecher, on account of an accident, ligated the descending branch of the

[1] Cited by Amenomiya, loc. cit.

[2] Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, Arch. of Internal Medicine, 1909, iii, 476.

left coronary artery and the patient lived five days. Thorel has seen hearts with complete obstruction of the artery, with fibrous or calcified myocardium, and yet no symptoms during life, the patient dying of some other disease. I have seen the descending branch completely occluded with an extensive fibrous area in the interventricular septum and at the apex, the latter aneurysmally dilated, where the process was clearly one of long standing. West[1] cites several cases in which at autopsy complete obstruction of one coronary was found, yet the patients had long survived this serious lesion. Chiari, in a thirty-two-year-old nephritic, found a sclerosed right coronary plugged by a thrombus, with resulting scattered patches of myomalacia cordis in the areas supplied by this artery. A portion of this thrombus had become detached and had embolically plugged the left coronary, resulting in sudden death. From the symptoms and the autopsy findings the thrombus in the right artery had formed at least two days before. The fact that the softened patches in the myocardium were scattered, with normal tissue between, and that the heart functionated fairly well until the left artery also was obstructed leads Chiari to infer that anastomoses must exist between the right and left coronaries. Merkel[2] drew the same inference as to anastomoses from the patchy character of the lesions in the heart of a woman, aged seventy-six years, there being normal muscle between the softened areas. The left coronary was the seat of the obstruction. He also saw in a man, aged thirty-seven years, the left coronary closed, with nourishment through the right artery. Dock,[3] in a case of gradual occlusion of the right coronary artery, was able to demonstrate a direct opening of the finer branches of the left coronary into the end of the right.

Spalteholz says we all know cases of stoppage of large vessels without large infarcts resulting. Recklinghausen and Fujinami found this condition in man, as Hirsch had in dogs and monkeys, *i. e.*, smaller infarcts than the distribution of the vessels would lead one to expect. Galli saw complete closure of the entrance to

[1] Trans. Path Soc., London xxxiv, 67.
[2] Ueber den Verschluss der Kranzarterien des Herzens Festschrift für Rosenthal, Leipzig, 1906.
[3] Notes on the Coronary Arteries, Ann Arbor, 1896.

the right coronary artery yet no change in the myocardium. By injection he found a round-about anastomosis between the right and left coronary arteries. Samuelson cites a case living five hours after obstruction; Huber one living several days. Aschoff and Tawara[1] saw a patient live fourteen days, "with nearly complete infarction of the parietal wall of the left ventricle." Several cases of angina pectoris cited by Huchard[2] lived many hours after the onset of the final attack, which autopsy showed was due to a thrombotic closure of an artery. Osler refers to the fact that the patient may live for some time after obstruction. Krehl expressly states that in man the more or less sudden occlusion of an entire coronary artery, or at least a large branch, such as the descending branch, is compatible with a continuance of life.

One may conclude, therefore, from a consideration of the clinical histories of numerous cases where there has been careful autopsy control, from animal experiments and from anatomical study, that there is no inherent reason why the stoppage of a large branch of a coronary artery, or even of a main trunk, must of necessity cause sudden death. Rather may it be concluded that while sudden death often does occur, yet at times it is postponed for several hours or even days, and in some instances a complete, *i. e.*, functionally complete, recovery ensues.

The clinical manifestations of coronary obstruction will evidently greatly vary, depending upon the size, location, and number of vessels occluded. The symptoms and end results must also be influenced by blood pressure, by the condition of the myocardium not immediately affected by the obstruction, and by the ability of the remaining vessels properly to carry on their work, as determined by their health or disease. No simple picture of the condition can, therefore, be drawn. All attempts at dividing these clinical manifestations into groups must be artificial and more or less imperfect. Yet such an attempt is not without value, as it enables one the better to understand the gravity of an obstructive accident, to differentiate it from other conditions presenting

[1] Die Heutige Lehre von den Pathologisch-Anatomischen Grundlagen der Herzschwache, Jena, 1906, p. 56.

[2] Traite Clinique des Maladies du Cœur, second edition, p. 560.

somewhat similar symptoms, and to employ a more rational therapy, that may, to a slight extent at least, be more efficient.

The variations in the results are to be accounted for in part by variations in the freedom with which anastomosing branches occur. Presumably, too, symptoms will vary with the vessel or branches occluded. It is conceivable that with occlusion of the right coronary the symptoms might be different from those following obstruction of the left artery; systemic edema might be a consequence of the former condition and pulmonary edema of the latter. These points are, however, by no means settled either by experimental or clinical observation. The condition of the remaining vessels as to patency and presence of sclerosis must play an important part in deciding how much they are capable of doing in the way of compensatory nutrition to the anemic myocardium; the strength of the heart itself, as determined, perhaps, by old valvular or myocardial disease, would also have its influence. And presumably a sudden overwhelming obstruction, with comparatively normal vessels, would be followed by a profounder shock than where gradual narrowing of a lumen through sclerosis has accustomed the heart to this pathological condition, and has perhaps caused collateral circulation through neighboring or anastomosing vessels to be compensatorily increased. The influence of the vessels of Thebesius is also not to be overlooked in this connection; compensatory circulation through these accessory channels may be of considerable importance in nourishing areas of heart muscle poorly supplied by sclerotic or obstructed arteries.

Attempts to group these cases of coronary obstruction according to clinical manifestations must be more or less unsatisfactory, yet imperfect as the groups are, the cases may be roughly classified.

One group will include cases in which death is sudden, seemingly instantaneous, and perhaps painless. Krehl[1] has emphasized the peculiarities of the sudden death of this type, the lack of terminal respiratory agony, of distortion of the features, of muscular contractions.

A second group includes those where the attack is anginal, the

[1] Der Verschluss der Kranzarterien, in Nothnagel's System, xv. p. 369.

pain severe, the shock profound, and death follows in a few minutes or several minutes at the most.

In a third group may be placed non-fatal cases with mild symptoms. Slight anginal attacks without the ordinary causes such as walking, perhaps some of the stitch pains in the precordia, may well be due to obstruction of small coronary twigs. Such an interpretation of these phenomena is, however, only a surmise based upon the fact that other causes for the pains are lacking and that the patchy fibrosis of the myocardium that is later found at autopsy may have originated in obstruction of the sclerotic vessels, and such obstruction in small vessels may well have produced symptoms differing chiefly in degree from those caused by obstruction of larger arteries of the heart.

In a fourth group are the cases in which the symptoms are severe, are distinctive enough to enable them to be recognized as cardiac, in which the accident is usually fatal, but not immediately so, and perhaps not necessarily so. It is to the clinical features of this group that attention is directed in what follows.

By way of introduction, I give in outline the history of a case, experience with which acutely attracted my attention to this subject.

A man, aged fifty-five years, supposedly in good health, was seized an hour after a moderately full meal with severe pain in the lower precordial region. He was nauseated, and, believing something he had just eaten had disagreed with him, he induced vomiting by tickling his throat. The pain continued, however, and his physician was called, who found him cold, nauseated, with small rapid pulse, and suffering extreme pain. The stomach was washed out and morphine given hypodermically. The pain did not cease until three hours had passed. From this time the patient remained in bed, free from pain, but the pulse continued rapid and small, and numerous rales appeared in the chest. When I saw him twelve hours from the painful attack there was a clear, calm mind, a moderate cyanosis, a mild dyspnea, a chest full of fine and coarse moist rales, a running, feeble pulse of 140. The heart tones were very faint, and there was a most startling and confusing hyper-resonance over the chest, the area of heart dulness being

entirely obscured. The abdomen was tympanitic. The urine was scanty, of high specific gravity, and contained a small amount of albumin and a few casts. The temperature was subnormal, later going to 99°. Occasionally there was nausea and twice a sudden projectile vomiting of considerable fluid material. This condition remained with slight variations up to the time of his death, fifty-two hours after the onset of the pain, though at one time the rales seemed nearly to have disappeared. A few hours before death the patient described a slight pain in the heart region, but said it did not amount to much. A remarkable circumstance, and one that occasioned surprise in those who saw him and who realized from the almost imperceptible pulse and the feeble heart tones how weak the heart must be, was the fact that the patient frequently indulged in active muscular effort without evident harm. He rolled vigorously from side to side in the bed, sat suddenly bolt upright, or reached out to take things from the nearby table, and once, feeling a sudden nausea, jumped out of bed, dodged the nurse, and ran into the bathroom, where he vomited; and yet he seemed none the worse for these exertions.

At autopsy (Dr. Hektoen) the heart was of normal size, but both coronary arteries were markedly sclerotic, with calcareous districts and narrowing of the lumen. A short distance from its origin the left coronary artery was completely obliterated by a red thrombus that had formed at a point of great narrowing. The wall of the left ventricle showed well-marked areas of yellowish and reddish softening, especially extensive in the interventricular septum. At the very apex the muscle was decidedly softer than elsewhere. The beginning of the aorta showed a few yellowish spots, these areas becoming less marked as the descending part was reached. An acute fibrinous pericardial deposit, which showed no bacteria in smears, was found over the left ventricle. (The pericarditis probably explains the slighter pain complained of a few hours before death.) There was marked edema of the lungs. In other respects the anatomical findings were those of health.

A colleague personally related to me the case of a man, aged sixty years, who, three days after a severe anginal seizure, felt well enough to walk on the street, though with some dyspnea. He died

suddenly on the fifth day. The obstruction in the left coronary, and the muscular softening found at autopsy were similar to those in the case described.

Since my attention has been called to this condition, I have seen five other cases that I am convinced were instances of coronary thrombosis, the patients living many hours after the accident, though no autopsy control confirms this opinion. All were men beyond fifty years. In all there was some evidence of peripheral arteriosclerosis; all had had previous anginal attacks. In all the final attack was described as the severest and most prolonged in the experience of the patient. Morphine alone had given relief. In all the sudden development of a weak pulse, with feeble cardiac tones, was a striking feature; the pulse was generally rapid. Dyspnea and cyanosis varied in degree. Rales, moist and dry, were usually present. Emphysema was present to a moderate degree in 2 of the 5. Only 1 patient left his bed after the attack. His pulse showed great improvement as to quality and rate, though dyspnea, rales, edema of the legs, albumin, increased area of cardiac dulness, etc., showed failure of the heart muscle. From the time of the seizure, *i. e.*, the time of the obstruction, to death was in 1 case three days, in 1 seven, in 2 twelve, and in 1 twenty days.

One of these cases is, it seems to me, a typical one of this sort, and, though autopsy is lacking, I venture to give the history.

The patient was a man, aged sixty-five years, of exemplary habits. His health had been good up to three years before, when he noticed at times a tight feeling in the precordia on walking. For the last three months typical anginal seizures often compelled him to stop after walking two or three blocks. Three days before he had had a moderately severe angina.

Thirty-six hours ago, in the night, he made a noise, awakening his wife. For a few seconds he was, perhaps, unconscious. He complained of unbearably severe pain in the upper stomach region; the pain did not radiate. He was nauseated and belched gas freely. His physician saw him inside of twenty minutes, gave bicarbonate of soda, which was vomited. The pain continuing, a hypodermic of morphine was necessary. The patient was pale, covered with

cold sweat, and had a small, rapid pulse. His appearance was that of collapse. His distress seemed to him largely abdominal.

When I saw him his color had returned and he was ruddy-cheeked. He complained of extreme weakness. His mind was clear. There was a little cyanosis, and respiration was somewhat labored. There were numerous rales in the chest. The pulse was 110 and small. The heart tones were faint; there was no murmur. The heart was a trifle enlarged, as it had been for some years. The area of cardiac flatness was decidedly small on account of overlying lung. The liver dulness was but a narrow band along the costal margin; the edge of the liver could be palpated. No spleen could be made out. The urine contained a distinct ring of albumin and a few granular and hyaline casts. There was a doubtful faint trace of bile. On digalen and nitroglycerin there seemed to be some improvement in the quality of the pulse.

At a second visit the condition was much the same. There had been a few spells of more marked oppression in breathing, with some increase in cyanosis and weakness of the pulse.

At a third visit, October 19, 1910, it was learned that he had had a bad night, with severe spells of dyspnea. The pulse had been but barely perceptible at the wrist and beat 120 to the minute. At 5 A.M. both the physician and the patient himself had felt that death was at hand. He had rallied, however, and when I saw him was conscious, with very feeble pulse of 110, and barely perceptible heart tones. He was extremely weak. Breathing was of the Cheyne-Stokes type. The patient seemingly dozed during apnea, yet answered questions. What I took to be a faint pericardial friction could be made out over the lower left sternal border. The patient said he was not in pain. He declared he got relief from swallowing orange juice, which he repeatedly sipped. He remained in this condition for sixteen hours longer. From the onset of his severe anginal attack to death was seven days.

The case of Professor Panum is instructive and is described by Fraentzel.[1] For a few weeks Panum had noticed dyspnea and a tight feeling on going up stairs. May 1, 1885, coming home in

[1] Krankheiten des Herzens, Berlin, 1892, iii, 51.

the wind, he stopped often, and on reaching home had a sudden, severe, tearing pain in the precordia, running out to the left arm and fingers. The pulse became rapid, small, and irregular. He broke out into a profuse sweat. He was nauseated and induced vomiting by tickling his throat. The physical findings are not accurately known. The mind was clear to the last. He died suddenly about fourteen hours after the onset of symptoms. At autopsy both upper lobes of the lungs and the middle lobe were found emphysematous. The left coronary artery was atheromatous, narrowed, and a white soft thrombus was attached to the wall. The musculature of the left ventricle was degenerated and softened and had ruptured just to the left of the septum.

Engelhardt[1] describes the case of a man, aged fifty-four years, in whom, after a thrombosis of the left coronary artery with suddenly developing gastric and abdominal symptoms, there was an illness of eight days, with fever, meteorism, vomiting, oppression, and then in a tachycardial attack rupture of the anterior wall of the left ventricle, with hemopericardium. Death twelve hours after the rupture. The symptom-complex resembled the picture of the abdominal-pectoral vascular crises (Pal).

A study of cases of this type shows that nearly all are in men past the middle period of life. Previous attacks of angina have generally been experienced, though, as shown by my first case, the fatal thrombosis may bring on the first seizure. The seizure is described by patients who have had previous experience with angina as of unusual severity and the pain persists much longer. In some instances there has been no definite radiation of the pain, as to the neck or left arm, though this may have been a feature of other anginal attacks, and the pain, as in these two cases, may be referred to the lower sternal region or definitely to the upper abdomen. Cases with little or no pain have been described. In Chiari's case the pain is not referred to, the patient, though with slow, irregular, and weak pulse, being out of bed. The obstruction of the right coronary was, as Chiari says, "so to speak latent." Thorel also refers to a painless case. Some of Huchard's

[1] Ein Fall von Herzruptur, Deutsch. med. Woch., 1910, xxxv, No. 19, 838.

cases with obstruction did not show anginal pain. Nausea and vomiting, with belching of gas, are common. There may be tympany. Ashy countenance, cold sweat, and feeble pulse complete the picture of collapse. The attention of the patient and the physician as well may, therefore, be strongly focussed on the abdomen, and some serious abdominal accident be regarded as the cause of the sudden pain, nausea, and collapse. The cardiac origin may be the more easily overlooked when there has been no previous typical angina, and when, as may happen (Case I), there is no arteriosclerosis manifested peripherally and no enlargement of the heart to be made out.

Cohnheim found in dogs that the pulse after obstruction was slow. This may be so in the thrombotic obstruction of disease in man. But a rapid pulse is frequently seen. The pulse may be irregular. A striking feature has been its weakness. In 2 patients I have seen a rapid, thready, almost imperceptible, radial pulse, of such a quality that if met with in pneumonia or typhoid fever it would have warranted one in presaging death within a few minutes or hours. Yet one patient lived forty hours and another four or five days with a pulse of this quality. In Hammer's[1] case the pulse dropped from 80 to 8 per minute, the patient living thirty hours from the onset of the symptoms that marked the closure of the right coronary opening. Blood pressure is low. The heart tones have been feeble, in fact often startlingly feeble. Feeble contraction of the weakened anemic heart muscle accounts for the weak pulse and the weak tones. Still another reason for the faint tones is found in the acute emphysema—*Lungenschwellung* and *Lungenstarrheit* of von Basch—by which condition the heart sounds are obscured by overlapping air-containing lungs. This also makes it difficult to map out the outlines of the heart, and, coupled with the feeble apex impulse, may make such an examination for the size of the heart very unsatisfactory.

Dyspnea and cyanosis have been variable at times, much less than one would expect from the character of the accident and the quality of the heart's action. Rales, dry and moist, have been

[1] Wiener med. Woch., 1878, No. 5.

present in many cases, in some, as in my first case, largely moist, diffuse, not very large. Here there was a moderate amount of thin, frothy, slightly blood-tinged fluid expectorated, as in edema of the lungs, which condition was found at the autopsy. I mention this because some, with Cohnheim, contended that the conditions for edema would not be produced by coronary obstruction, as both right and left heart ceased beating simultaneously. Others, *e. g.*, Samuelson, Bettelheim, and Michaelis found edema. My case shows such edema. Possibly the right heart may have remained relatively stronger than the left after the accident, and so Welch's condition for edema have been presented.

The weakness of the heart and the low blood pressure will account for the scanty urine and the trace of albumin. A palpable liver may likewise owe its enlargement to passive congestion.

Nearly always the mind is clear, at times unusually clear, until toward the last. Some patients seem conscious, as is so common with angina, that they are face to face with death, but in none that I have seen has there been uncontrollable fear or the restlessness of fright. The seriousness of the accident seemed to be realized, but there was no panic. Perhaps the relief from the agony of the initial pain causes an unnatural mental calmness.

General weakness has been marked in some cases, in others not. One patient showed for more than a week an asthenia comparable to that of the terminal stage of pernicious anemia or of Addison's disease. He hesitated to move in bed for the further reason that even turning on the side caused him the sensation as though the heart were giving out. Even slight movement caused some pain. His case is representative of the type of status anginosus. Obrastzow regards this as the usual manifestation of coronary thrombosis. My experience shows that such obstruction may be followed by a complete cessation of pain for hours and even to the time of death. Some of these patients of the latter type will, if permitted, move freely or even get out of bed.

The occurrence of a serofibrinous exudate over the area of myocardial softening, with roughening of the pericardium, has been noted in several instances. This may explain a later precordial distress, as in Case I. A fine pericardial friction, therefore, occurring

several hours or a few days after the initial pain, may be confirmatory evidence of coronary obstruction. Osler[1] concluded in one of his cases of angina that the attack was probably associated with acute infarct of the ventricle, "as a pericardial rub was detected the next day." Dock recognized this pericarditis *intra vitam* in one of his cases and found it post mortem over the softened area. In one of Leyden's cases that lived five days from the onset of symptoms of dizziness, faintness, small pulse, there was found myomalacia cordis, and especially at the apex, where a softened area reached to the surface, there was pericarditis; cloudy fluid was in the pericardial sac. This was almost certainly a case of coronary obstruction, though the occluding lesion is not described. This pericarditis is in keeping with some of the experimental work on lower animals, *e. g.*, that of Bickel, who in his dogs, killed nineteen and seventy days after ligation, found localized pericarditic adhesions over the area representing the myocardial softening.

Death is the result in nearly all of these cases. Yet it may be delayed for many days. More than this, there is, as has been shown by reference to experimental work, no intrinsic reason why some patients with obstruction of even large branches of the coronary artery may not recover. Experimental animals sometimes do. And, as already said, mild cases must occur, and one cannot pretend to say where the dividing line should be drawn between the mild obstruction of a coronary branch, whose recovery means a few fibrous patches in the myocardium, and the more serious one that in a few days is to lead to rupture of the heart or is to produce an extensive weakened fibrous area that will ultimately yield in cardiac aneurysm. Death may then be caused by rupture, by sudden asystole, or by gradual giving out of the weakened heart muscle, or by "ingravescent systole," as Balfour[2] styles it, a mode of death occupying from half an hour to a week, illustrated by one of his cases where death occurred one week after the obstruction which was found post mortem. In one instance, in which I believe the anginal seizure was thrombotic, a dilatation of the heart, with orthopnea, dropsy, etc., followed the seizure. Death

[1] Lumleian Lectures on Angina Pectoris, Lancet, March 12 and 26, and April 9, 1910.
[2] Clinical Lectures on Diseases of the Heart, 1898, third edition, pp. 316 and 328

here was as in cardiac failure from other causes. Some of the dogs of Miller and Matthews died in this way several weeks after the ligation of the coronary. Where the heart slowly wears out in the course of a few days, Cheyne-Stokes respiration, general asthenia, urinary scantiness, with mental apathy and exhaustion, may be present.

Emphasis ought to be laid on the resemblance of some of these cases to surgical accidents. The sudden onset of pain over the lower sternal and epigastric region, the nausea and vomiting, the tympany, the feeble pulse, ashy color, cold sweat, and other signs of collapse make one think of such conditions as gall-bladder disease, acute hemorrhagic pancreatitis, perforation of gastric or duodenal ulcer, hemorrhage into the suprarenal capsule, etc. The dyspnea, hyper-resonant thorax, obscured heart tones, may suggest pneumothorax or diaphragmatic hernia. In my first case, while the diagnosis made was that of cardiac accident, there were so many disquieting features that surgical counsel was called to reassure one that some surgical accident, such as those enumerated, had not been overlooked. Details as to differential diagnosis need not be given. Where there is arteriosclerosis, enlarged heart, a history of previous angina, typical radiation of the pain to the neck and arm, the diagnosis will not be so difficult as where these suggestive aids are lacking. The bilateral character of the emphysema, the persistence of breath sounds, often with rales, the failure of the heart to be dislocated, will help exclude pneumothorax and diaphragmatic hernia. The absence of blood from the vomitus, the absence of peritonitic tenderness, a study of the temperature, the leukocytes, etc., will help in excluding subdiaphragmatic accidents.

Obrastzow[1] calls particular attention to this resemblance to surgical accidents which our own experience corroborates. Engelhardt's case also illustrates this point.

If these cases are recognized, the importance of absolute rest in bed for several days is clear. It would also seem to be far wiser to use digitalis, strophanthus, or their congeners than to follow

[1] Obrastzow and Straschesko, Zur Kenntniss der Thrombose der Koronararterien des Herzens, Zeit. f. klin. med., 1910, lxxi, 116.

the routine practice of giving nitroglycerin or allied drugs. The hope for the damaged myocardium lies in the direction of securing a supply of blood through friendly neighboring vessels so as to restore so far as possible its functional integrity. Digitalis, or strophanthus, by increasing the force of the heart's beat, would tend to help in this direction more than the nitrites. The prejudice against digitalis in cases where the myocardium is weak is only partially grounded in fact. Clinical experience shows this remedy of great value in angina, and especially in cases of angina with low blood pressure, and these obstructive cases come under this head. The timely use of this remedy may occasionally in such cases save life. Quick results should also be sought by using it hypodermically or intravenously. Other quickly acting heart remedies would also be of service.

DISCUSSION

Dr. E. Libman: I have been in the habit of classifying the lesions we generally meet in the coronary arteries as follows: Besides the recent thromboses and embolisms there are cases with partial or complete obstruction by plaques. These are especially to be found in men who have been heavy cigar smokers. If the occlusion by the plaque is incomplete, it may be made complete by a thrombus. In some cases the symptoms are due to a narrowing of the orifices of the arteries by plaques due to atherosclerosis or by puckering.

Some cases with closure of the coronary artery live not only for weeks but for months. They present a remarkable facial appearance from which the diagnosis can in some cases be adduced. They have a peculiar dirty ashen color; Sansom referred to it as "a leaden overcast" (but he believed it to be due to disease of the aorta itself). It is valuable to recognize the condition, when possible, because such patients are apt to succumb at any time, and particularly after operative procedures.

The observations of Dr. Herrick on pericarditis following attacks of angina are of great interest. Kernig has described such cases under the name of epistenocardial pericarditis, and ascribes to this condition the febrile reaction which sometimes comes on after attacks of angina pectoris.

LYMPH FORMATION AND EDEMA OF THE LIVER WITH EXPERIMENTAL NEPHRITIS (CANTHARIDIN)

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Experimental production of nephritis has offered a means of explaining the pathogenesis of nephritis and its associated phenomena not afforded by methods applicable to patients suffering with the disease. The possibility that changes in the liver have a part in the functional disturbances which accompany nephritis, has been suggested by the occurrence of edema of liver and gall-bladder in association with nephritis produced by a substance capable of causing acute nephritis in man, namely, cantharidin. An attempt to analyze the factors upon which this hepatic edema depends, has shown that the poison exerts an important influence upon the production and flow of lymph. Experiments with other renal poisons, as yet incomplete, have shown that they exert an important influence both upon the liver and upon the flow of lymph. The present article will be limited to a discussion of the changes caused by cantharidin.

The experimental studies of Heidenhain[1] upon lymph formation, define two groups of substances which increase the production of lymph. Heidenhain's lymphagogues of the first order, include a variety of protein substances such as peptone, extracts from the tissues of certain invertebrates, namely, extract of muscle of crab, extract of head and body of the leech, egg albumen and other

[1] Pflüger's Arch. f. Physiol., 1891, xlix, 209.

substances. When injected into the circulation of the dog, they cause an acceleration of the flow of lymph from the thoracic duct. This increase begins immediately after injection and lasts an hour or more; the lymph contains an increased quantity of protein though its content in inorganic salts remains unchanged. Ten cubic centimeters of an aqueous extract of crab meat may increase the flow of lymph sixfold and increase its protein content from 4.06 to 5.57 per cent.; a solution of peptone causes an even greater acceleration of the flow of lymph. Heidenhain's lymphagogues of the second order are crystalloid substances; among those which he has tested, are grape sugar, sodium chloride and sodium sulphate. Such substances injected into the circulating blood may increase the flow of lymph from the thoracic duct and this lymph contains less protein than the normal lymph from the thoracic duct. Heidenhain cites experiments which indicate that the increased flow caused by lymphagogues of the first order is dependent upon the vital activity of the endothelial lining of the bloodvessels, whereas the action of crystalloids is dependent upon well known physical forces produced by changes in the concentration of the blood and tissue fluids. Lymphagogues of the first order cause no increase of urinary excretion, whereas crystalloids increase the flow of urine.

Starling[1] found that increase of lymph flow from the thoracic duct caused by peptone or by decoction of the muscle of crawfish may be almost completely prevented by ligation of the portal lymphatics. He attributes the entire increase to lymph derived from the liver and suggests that the small increase of flow which occurs after ligation of the portal lymphatics is referable to flow through those lymphatic channels which accompany the hepatic vein. Starling has found an increase of pressure in the portal vein following injection of so-called lymphagogues of Heidenhain's first order, but since increased lymph flow continues after portal pressure has fallen, he believes that increased permeability of the capillaries of the liver has an important part in bringing about increased flow of lymph.

[1] Jour. of Physiol., 1894, xvi, 224; 1894, xvii, 30.

The capillaries of the liver, according to Starling, are more permeable than those in other tissues. Lymph obtained from the liver contains approximately from 6 to 8 per cent. of solids, whereas lymph from the intestine contains from 4 to 6 per cent., and lymph from the extremities only from 2 to 4 per cent. The capillaries of the liver are extremely sensitive to pressure, an elevation of pressure in the hepatic vein equal to 200 mm. of water produced by obstruction of the vena cava above the diaphragm causes an enormous flow of lymph derived from the liver.

The permeability of the hepatic capillaries demonstrated by the studies of Heidenhain, Starling, and others gives significance to the occurrence of edema of the liver produced by cantharidin. This substance, it is well known, produces changes in the kidney accompanied by albuminuria. At the end of one hour after the injection of from 0.005 to 0.02 gram cantharidin into rabbits, Cornil and Brault[1] found an accumulation of material containing nucleated cells within the capsular space of the Malpighian bodies of the kidney. Later, according to their observations, cells lining the capsule are swollen and undergo desquamation. The cells of the convoluted tubules become swollen and their protoplasm is granular and vacuolated; within the lumina there is granular debris. With poisoning caused by repeated administration of small doses of cantharidin, round cells accumulate about the arteries. Eliaschoff[2] observed similar changes; in the capsular space were albuminous precipitate and cells regarded as swollen white corpuscles; swelling and desquamation of the capsular epithelium were found. The renal tubules exhibited degenerative changes. In white rats poisoned with cantharidin Welch[3] found that the cells accumulate in the capsular space. He does not regard these cells as swollen leukocytes which have emigrated from the bloodvessels nor as desquamated epithelial cells, but thinks that they are cells of the convoluted tubules which have been pushed back into the glomerular space. Lyon[4] has observed the same change; he has

[1] Cornil and Brault, Etudes sur la pathologie du rein, Paris, 1884. Quoted by Lyon.
[2] Virchow's Arch., 1883, xciv, 323.
[3] Trans. Assoc. Amer. Phys., 1886, i, 171.
[4] Jour. of Path. and Bact., 1904, ix, 400.

noted that the capsular space is devoid of contents, in animals which survived longer than ten hours, the tuft filling it almost completely. Lyon found advanced degeneration in the tubules; the ascending limb of the loop of Henle may exhibit coagulative necrosis. The convoluted tubules are dilated and the inner parts of the cells undergo disintegration leaving a basal part containing a nucleus which may stain deeply. The cells of the collecting tubules are swollen and granular, particularly in the larger tubules, and have frequently undergone desquamation into the lumen. Polynuclear leukocytes are often found between these cells. Casts are formed within the collecting tubules particularly within the medullary rays. With less acute poisoning, lymphocytes may collect about bloodvessels.

Schlayer and Hedinger,[1] using physiological methods, have described experiments which they believe indicate the occurrence of two types of experimental nephritis, one caused by potassium chromate or uranium nitrate, and referable to changes in the tubules of the kidney, and the other caused notably by cantharidin or arsenic, and referable to changes in the glomeruli. Alteration of glomeruli is demonstrable by vascular reactions rather than by anatomical changes in the capillaries or epithelium of these structures. Animals with nephritis following the administration of potassium chromate or uranium nitrate eliminate an increased quantity of urine and exhibit a variety of reactions which demonstrate that the bloodvessels of the kidney retain their normal excitability to certain stimuli; the oncometer shows that transient sensory stimulation or administration of adrenalin causes the bloodvessels to contract with somewhat abnormal activity, whereas caffein or strong salt solution causes dilatation somewhat greater than that which occurs with administration of the drug in normal animals; phloridzin causes the polyuria and glycosuria observed after its administration to normal animals. In animals which have received cantharidin or arsenic, similar tests applied within from four to eight hours show that the vascular apparatus of the kidney has undergone profound alteration. A diminished quantity

[1] Deutsches Arch. f. klin. Med., 1907, xc, 1.

of urine is excreted; contraction and dilatation of the vessels under the conditions which have been named are diminished or absent; phloridzin cause no polyuria and no glycosuria.

After the injection of from 0.013 to 0.026 grams of cantharidin dissolved in ethyl acetate (1 to 2 c.c. of a solution containing 0.2 gram cantharidin in 15 c.c. ethyl acetate) into dogs ranging in weight from 2.5 to 10 kilos, I have found that the changes observed after death are fairly constant. Small animals are killed by 0.013 gram of cantharidin, but larger animals survive this dose. Death with the hepatic changes, which will be described, may occur within five hours. The kidneys are slightly enlarged, succulent, and deep red throughout; the medullary rays are conspicuous at times as gray markings. Microscopic examination shows the profound alterations in the convoluted tubules described by Welch, Lyon, and others. Particularly noteworthy are the consequent changes within the glomeruli. The capsular space is dilated and contains both granular material, consisting of albuminous precipitate and hyaline droplets, and large nucleated cells, often in excellent preservation. The protoplasm of such cells is identical in appearance with that of the cells which compose the adjacent convoluted tubules. Their nuclei are often irregular in shape; at times the nuclei stain intensely, at times they remain almost unstained. Favorable sections passing through the junction of glomerular capsule and its convoluted tubule show that the cells within the capsule are continuous with those of the tubule which occasionally project as a rounded mass without obvious lumen through the neck of the capsular space. The epithelium of the capsule and of the glomerulus exhibits no alteration.

Coincident with the changes which occur in the kidneys, there are noteworthy changes in the liver and gall-bladder. The liver is turgid and homogeneously deep red without lobular markings. Blood in great abundance escapes from its cut surface. The gall-bladder is swollen and bluish gray in consequence of edema of its wall, which may be two or three millimeters in thickness. The cellular tissue between the gall-bladder and the liver is conspicuously edematous. Widely dilated lymphatics, often 1.5 mm. in diameter, accompany the structures contained in the portal spaces and pass

downward from the root of the liver through the gastrohepatic omentum to the regional lymphatic nodes, which are situated at the base of the duodenal mesentery and in the gastrohepatic omentum along the upper margin of the splenic arm of the pancreas. Similarly dilated lymphatics connect adjacent nodes. The afferent lymphatics of these nodes usually contain blood-tinged lymph and end upon the surface of the node, of which the peripheral sinus and medulla are stained red.

The lymphatic nodes which become swollen and edematous are as follows: (1) A large node situated at the base of the duodenal mesentery in contact with the superior mesenteric vein immediately below its junction with the splenic. (2) One, two, or occasionally more smaller nodes situated in the duodenal mesentery between its base and the duodenal arm of the pancreas; these nodes are occasionally in almost immediate contact with a group of large nodes at the base of the cecum. (3) From two to six lymphatic nodes situated in contact with the splenic vein in the mesenteric fold which is attached to the superior margin of the splenic arm of the pancreas. The largest of these nodes is that which is nearest the liver; it is in almost immediate contact with another large node, *i. e.* (1), which is adjacent to the superior mesenteric vein.

Microscopic examination of the liver demonstrates that edema of the gall-bladder is part of a general edema of the liver. The tissue of the portal spaces is distended and its interstices contain albuminous coagulum; lymphatic vessels are dilated. There is similar edematous distention of the tissues above the central and sublobular veins. Dilated lymphatics contain coagulated lymph in which red blood corpuscles are numerous. Within the parenchyma of the lobules the endothelium of the capillaries is separated by wide spaces from the adjacent columns of liver cells and in these spaces red blood corpuscles are numerous.

Edema of the gall-bladder affects the serous more than other coats of the wall. In the serous coat and in the loose tissue in contact with the under surface of the liver are immensely dilated lymphatics which are constricted at intervals by circular valve-like folds.

Enlargement of the regional lymphatic nodes of the liver is in considerable part the result of immense dilatation of the sinuses and especially of those within the medulla. Here red blood corpuscles, lymphocytes, and large mononuclear cells are abundant. Cells showing various stages of disintegration are numerous; some have lost their nuclei, whereas others contain deeply stained nuclear fragments. Within such sinuses, fibrinous coagulum forms a network with fine meshes. It is obvious that fibrin formation has begun about injured cells, many of which still retain the characters of large mononuclear cells, for from these cells radiate in every direction fibrils of fibrin. In some instances a pale ill-defined nucleus is surrounded by a radiating mass of fibrils which appear to have replaced the protoplasm of the cell. Within the medullary cords and in the cortex of the nodes, destruction of cells is further shown by abundant nuclear fragmentation occurring with greatest frequency in large cells with abundant protoplasm. In the germinating centres of the cortex, necrosis of cells with fragmentation of nuclei is particularly advanced.

Observations of Starling which have shown that the increased flow of thoracic lymph caused by the action of Heidenhain's lymphagogues of the first order, namely, peptone, decoction of muscle from certain invertebrates, such as crab, crawfish, etc., is derived from the liver, have suggested that edema of the liver caused by cantharidin is referable to increased flow of lymph from the liver. It is noteworthy, on the contrary, that administration of the substances employed by Heidenhain, is not followed by edema. To determine the effect of cantharidin upon the flow of lymph from the thoracic duct a cannula has been inserted into the duct exposed near its termination at the junction of the subclavian and jugular veins and the flow of lymph has been measured during periods of ten minutes. Animals have been etherized during the entire course of the experiment which has been limited by the death of the animal to a period not exceeding three hours. At the end of this time, edema of the gall-bladder has been repeatedly well advanced.

Diminution of the flow of thoracic lymph usually occurs within a period of from twenty to thirty minutes after intramuscular injection of cantharidin accompanied by gentle kneading of the

injected muscle. In the two following experiments the flow of lymph from the thoracic duct has been retarded and edema of the gall-bladder has been noted at the end of two and of three hours respectively.

EXPERIMENT I. Dog, weighing 10,800 grams; a cannula was inserted into the thoracic duct; after observation of the lymph flow during thirty minutes, cantharidin, 0.02 gram, was injected into the muscles of the thigh.

Time.	Lymph in c.c. per 10 minutes.	Remarks.
12.40–12.50	6.65	
12.50– 1.00	4.3	
1.00– 1.10	4.35	
		At 1.10 cantharidin, 0.02 gram, intra-
1.10– 1.20	4.0	muscularly.
1.20– 1.30	2.7	
1.30– 1.40	0.05	
1.40– 1.50	0.02	
1.50– 2.00	0.07	
2.00– 2.10	0.01	
2.10– 2.20	6.34	Abdomen opened and intestines disturbed.
2.20– 2.30	3.4	Lymph is tinged with blood.
2.30– 2.40	2.05	
2.40– 2.50	1.1	
2.50– 3.00	0.2	
3.00– 3.10	1.2	
3.10– 3.20	1.25	
3.20– 3.30	1.5	
3.30– 3.40	1.0	
3.40– 3.50	0.3	
3.50– 4.00	0.1	
4.00– 4.10	0.1	
4.10– 4.20	0.05	

The animal was killed at 4.27 P. M., three hours and seventeen minutes after injection of cantharidin.

Autopsy. The liver is red; the gall-bladder is edematous; conspicuous dilated lymphatics extend from the liver to the lymphatic nodes situated in the duodenal mesentery near its base and along the upper margin of the splenic arm of the pancreas. Microscopic examination of the liver shows edema, escape of red blood corpuscles, and dilatation of lymphatics. These nodes are enlarged and, with the surrounding tissue, edematous. The kidney is cloudy in appearance; the medullary rays are conspicuous.

Experiment II. A cannula was placed in the thoracic duct of a dog weighing 7600 grams. A record of the quantity of lymph obtained during periods of ten minutes is given below. After noting the flow during thirty minutes, 0.02 gram of cantharidin was injected into the muscles of the thigh.

Time.	Lymph in c.c. per 10 minutes.	Remarks.
11.05–11.15	0.8	Lymph opaque and white.
11.15–11.25	1.3	
11.25–11.35	2.5	
		At 11.25 cantharidin, 0.02 gram, was injected.
11.35–11.45	1.3	
11.45–11.55	2.1	Lymph tinged with blood.
11.55–12.05	1.3	
12.05–12.15	1.0	
12.15–12.25	0.7	
12.25–12.35	0.6	
12.35–12.45	0.35	
12.45–12.55	0.9	
12.55– 1.05	1.5	Lymph yellow and almost clear.
1.05– 1.15	1.75	
1.15– 1.25	2.1	
1.25– 1.35	1.45	Death occurred at 1.35

Autopsy. The liver is homogeneously deep red. The wall of the gall-bladder is thickened by edema and there is edema of the gastrohepatic omentum, of the duodenal mesentery, and of the tissues about the ileo-cecal and mesenteric lymphatic nodes. Microscopic examination of the liver shows edema with escape of red blood corpuscles and dilatation by lymphatics. The hepatic regional lymphatic nodes in the duodenal mesentery near its base and along the upper margin of the splenic arm of the pancreas are enlarged and edematous.

The kidney is deep red; the medullary striæ are conspicuous. Urine in the bladder contains no albumin, remaining clear when boiled and acidified; it causes an atypical reduction of Fehling's solution, but does not ferment.

In these experiments, administration of cantharidin has been followed by almost complete cessation of the flow of lymph. Although it has been possible to follow the changes which are caused by the poison during only three hours, advanced edema of the liver and gall-bladder have been present. Such edema has been almost constantly observed when more prolonged action of the drug has

caused death within from five to fifteen hours. The histological character of the edematous tissue has been described.

In Experiment I, at 2.10 P.M., the abdomen was opened and the intestines were manipulated in order to examine the bile ducts and the duodenal mesentery. This disturbance of the intestines was immediately followed by temporary discharge of a considerable quantity of thoracic lymph. Starling[1] has observed that pressure upon the intestines liberates abundant lymph. This temporary flow in Experiment I serves to demonstrate that the otherwise almost total cessation of lymph flow is not the result of coagulation or other obstruction within the cannula or adjacent injured thoracic duct.

In the following experiment diminution of flow from the thoracic duct has followed almost immediately the administration of cantharidin, but diminution of flow has been irregular and temporary; some edema of the gall-bladder has been produced.

EXPERIMENT III. In a dog, weighing 7800 grams, a cannula was inserted into the thoracic duct. The foregoing experiment was repeated.

Time.	Lymph in c.c. per 10 minutes.	Remarks.
11.00–11.10	4.9	Lymph grayish white.
11.10–11.20	6.5	
11.20–11.30	7.0	
		11.30 cantharidin, 0.02 gram, intramuscularly.
11.30–11.40	3.4	
11.40–11.50	1.7	Lymph faintly red.
11.50–12.00	5.9	Lymph reddish in color.
12.00–12.10	2.8	
12.10–12.20	3.8	Lymph well-marked yellow.
12.20–12.30	4.5	
12.30–12.40	2.1	
12.40–12.50	4.4	Lymph deep yellow.
12.50– 1.00	4.3	Lymph deep brown yellow.
1.00– 1.10	4.9	
1.10– 1.20	4.3	
1.20– 1.30	5.4	
1.30– 1.40	6.3	
1.40– 1.49	4.9	Died.

[1] Jour. of Physiol., 1894, xvi, 224.

Autopsy. The liver shows no noteworthy abnormality; the gall-bladder is edematous in patches but is not uniformly swollen. The regional lymphatic nodes are swollen, red, and in part edematous. Dilated lymphatics pass from the liver to these nodes.

The urine from the urinary bladder contains a moderate amount of albumin. Reduction indicates the presence of 1.17 per cent. of sugar; the urine ferments.

In two experiments, which will be described, there has been temporary diminution of lymph flow following injection of the drug, whereas in a third experiment (Experiment VI) no diminution has occurred, yet in all of these experiments, after about one and a half hours, there has been a greatly increased flow of thoracic lymph. With this active flow of lymph, no edema of the gall-bladder or liver had occurred.

Experiment IV. Dog, weighing 13,400 grams. Cannula was inserted into the thoracic duct with considerable difficulty.

Time.	Lymph in c.c. per 10 minutes.	Remarks.
1.50–2.00	5.8	Lymph gray white.
2.00–2.10	11.2	
2.10–2.20	10.4	
		2.20 to 2.21, cantharidin, 0.052 gram, intramuscularly.
2.20–2.30	12.85	
2.30–2.40	11.7	
2.40–2.50	11.3	Lymph blood tinged.
2.50–3.00	7.9	
3.00–3.10	5.5	
3.10–3.20	4.2	
3.20–3.30	3.2	
3.30–3.40	3.2	
3.40–3.50	4.8	
3.50–4.00	6.1	
4.00–4.10	7.6	Lymph deep red.
4.10–4.20	9.9	
4.20–4.30	11.65	
4.30–4.40	12.9	
4.40–4.50	14.6	
4.50–5.00	14.0	
5.00–5.10	9.6	
5.10–5.20	5.2	Died.

Autopsy. Liver is deep red. There is no edema of the gall-bladder.

EXPERIMENT V. Dog, weighing 12,600 grams. A cannula was inserted into the thoracic duct.

Time.	Lymph in c.c. per 10 minutes.	Remarks.
12.50–1.00	6.2	Lymph opaque white.
1.00–1.10	5.3	
1.10–1.20	5.0	
1.20–1.30	4.9	
		1.30, cantharidin, 0.052 gram, intramuscularly.
1.30–1.40	4.6	
1.40–1.50	5.8	
1.50–2.00	2.0	
2.00–2.10	2.8	
2.10–2.20	2.6	
2.20–2.30	1.05	
2.30–2.40	3.1	Lymph faintly blood-tinged.
2.40–2.50	7.1	
2.50–3.00	7.6	Lymph markedly blood-tinged.
3.00–3.10	10.7	Lymph yellowish.
3.10–3.20	9.3	Lymph deeper yellow.
3.20–3.30	4.2	Lymph bright yellow. Death.

Autopsy. There is no edema of the gall-bladder.

In the following experiment, injection of cantharidin, as in Experiments IV and V, caused a well-marked increase in the flow of lymph, but this increased flow was not preceded by a period during which the flow was diminished.

EXPERIMENT VI. Dog, weighing 18,600 grams. A cannula was placed in the thoracic duct.

Time.	Lymph in c.c. per 10 minutes.	Remarks.
12.10–12.20	10.0	Lymph opaque, white, slightly blood-tinged.
12.20–12.30	11.8	
12.30–12.40	8.9	
		12.40, cantharidin, 0.02 gram, intramuscularly.
12.40–12.50	12.8	
12.50– 1.00	10.7	
1.00– 1.10	8.3	
1.10– 1.20	9.8	

Time.	Lymph in c.c. per 10 minutes.	Remarks.
1.20–1.30	9.8	
1.30–1.40	8.2	
1.40–1.50	10.3	Lymph blood-stained.
1.50–2.00	9.2	
2.00–2.10	12.9	
2.10–2.20	9.2	
2.20–2.30	18.0	
2.30–2.40	16.5	
2.40–2.50	18.8	
2.50–3.00	21.3	
3.00–3.10	19.5	
3.10–3.20	27.3	
3.20–3.30	21.4	
3.30–3.35	4.0	Died at 3.35.

Autopsy. The liver is moderately deep red. There is no edema of the gall-bladder. The regional lymphatic nodes are enlarged and have red centres. Dilated lymphatics pass from the liver to these nodes.

The experiments which have been described are confirmed by others in which similar results have been obtained. The effect of cantharidin upon the flow of lymph from the thoracic duct is as follows: (*a*) Intramuscular injection of a fatal dose (0.02 gram) is usually followed by well-marked diminution of the flow, which is evident after from twenty to thirty minutes and reaches a minimum at the end of about one hour; the lymph is tinged with blood. No subsequent rise occurs and there is edema of the liver recognizable within from two to three hours after injection. (*b*) In a second group of experiments occurring more frequently with larger doses of cantharidin (0.05 gram) an increased flow of lymph follows the retardation which has been noted or occasionally occurs without a preceding diminution of output. This increased flow, occurring after an interval approximately from one and one-half to two hours after injection of the drug, may greatly exceed the normal. The lymph is no longer tinged with blood but assumes a yellow color and coagulates slowly.

Within the period of observation permitted by the experiment larger doses more frequently demonstrate the lymphagogue action of the poison. With smaller doses the flow of lymph does not

recover from its primary depression. Dilatation of lymphatics and edema of the liver and gall-bladder occurs during the time when flow of lymph from the thoracic duct is diminished and is almost constantly observed when death is caused by acute poisoning with cantharidin. Edema of the liver furnishes evidence that there is increased lymph formation in the liver before this increased production causes an increased flow from the thoracic duct. Histological examination shows that obstruction to the lymph stream capable of producing simultaneously edema and diminished flow of thoracic lymph occurs within lymphatic channels and notably within the sinuses of the regional nodes of the liver.

Those nodes which receive lymph from the liver are accurately defined by the poison. Their situation has already been described; they become enlarged and their medulla assumes a deep red color. The nodes which are affected are connected with the liver by lines of dilated lymphatics passing downward from the liver and gall-bladder to the proximal nodes and hence from one node to the next. These lymphatics contain lymph deeply tinged with blood and their termination in the peripheral sinus of the node is well defined by similar localized discoloration.

Microscopic examination of the regional nodes removed from animals which have died with edema of the liver and gall-bladder during the period of diminished flow from the thoracic duct show that the afferent lymphatics and the sinuses of the node, notably the peripheral sinus, contain fibrin which usually forms a fine network, but occasionally occurs in more compact particles. Particularly noteworthy is the relationship of this fibrinous network to cells which have undergone degenerative changes. Cells of which the nuclei are pale and ill-defined or wholly lost form centres from which radiate fibrils of fibrin. A similar radiate arrangement of fibrin occurs upon the free surface of endothelial cells still attached to the walls of the sinus.

Within the widely dilated sinuses of the node, cells are very numerous, often closely packed together and connected by the fibrinous network which has been described. Large mononuclear cells similar to those which line the sinuses are particularly numerous and are mingled with lymphoid cells and polynuclear leukocytes,

the latter being present in moderate number. Cells exhibiting evidence of degeneration and necrosis, doubtless caused by the poison, are numerous; many exhibit nuclear fragmentation, whereas others have assumed a hyaline appearance and have lost their nuclei. The destructive action of cantharidin is best seen in the germinating centres of the cortex, where nuclear fragmentation is usually widespread.

The presence of red blood corpuscles outside the capillaries of the liver, within the hepatic lymphatics, and in the sinuses of the lymphatic nodes, is further evidence of the injurious action of the poison, which appears to affect notably endothelium of the bloodvessels and lymphatics. Phagocytosis of red blood corpuscles by the large mononuclear cells which have been mentioned is actively in progress two to three hours after administration of cantharidin. Clumping of red blood corpuscles upon the surface of these cells may have a part in plugging the sinuses of the regional hepatic nodes. In one specimen masses of red corpuscles were adherent to the surface of mononuclear phagocytes which had taken many red corpuscles into their substance. Such observations show that the cell does not move toward the red corpuscles and ingest it, but attracts the corpuscle and holds it. I have not determined whether the conspicious yellow color assumed by the lymph from the thoracic duct is referable to destruction of red corpuscles with setting free of hemoglobin or to the presence of bile liberated by the injured liver.

Progressive dilatation of lymphatics and of the sinuses of the lymphatic nodes finally overcomes the obstruction opposed by the fibrinous thrombi which are formed in these channels. Diminished coagulability of the lymph probably explains the cessation of progressive formation of fibrinous plugs. Increased flow of lymph often far exceeding the normal then follows the temporarily diminished output.

In order to determine the relationship of lymphatic nodes to changes which occur in the liver, the effect of cantharidin has been tested upon animals from which the regional hepatic nodes have been extirpated. Removal of these nodes may be followed by establishment of collateral lymphatic circulation through channels

which pass directly to the thoracic duct without intervention of lymphatic nodes. Nodes which have been overlooked at the time of operation undergo hypertrophy. Whereas in normal animals fatal cantharidin poisoning has been almost invariably followed by edema of the liver and gall-bladder. Edema has occurred in only one of three animals in which after extirpation of the regional nodes, death has followed administration of the drug.

In this instance there was edema of the liver, gall-bladder, and pancreas and accumulation of fluid in the peritoneal cavity; a large lymphatic node was found in the gastrohepatic omentum and numerous dilated lymphatics passed to it from the liver. This enlarged node had undergone the changes which have been described, the sinuses being plugged with fibrin.

Experiment VII. Dog, weighing 9800 grams. The abdomen was opened and all the lymphatic nodes which could be found in the gastrohepatic omentum, in the duodenal mesentery, and near the splenic vein along the upper margin of the splenic arm of the pancreas were removed. On the twenty-second day after operation cantharidin, 0.013 gram, was administered intramuscularly; on the following day, 724 c.c. of urine contained 4.16 grams of fermentable sugar and albumin in abundance; on the next day sugar was still present. On the twenty-sixth day, cantharidin, 0.006 gram, was administered; 550 c.c. of urine collected during the following day contained 2.43 grams of sugar and abundant albumin. On the thirtieth day cantharidin, 0.013 gram, was administered, and albuminuria but no glycosuria followed. On the fortieth day, cantharidin, 0.02 gram, was given; death occurred during the following night. The urine, 330 c.c., contained 3.52 grams of sugar (Benedict's method) and albumin determined by Esbach's method equal to 2.667 grams per liter.

Autopsy. The peritoneal cavity contains 23 c.c. of red serous fluid. The liver is deep red; the gall-bladder is edematous throughout, the wall measuring 2 to 3 mm. in thickness. Many dilated lymphatics filled with blood-stained lymph pass in parallel lines to a firm deep red lymphatic node 2 cm. in length situated in the gastrohepatic omentum at the margin of the foramen of Winslow. Two smaller blood-tinged nodes are found at the base of the duodenal mesentery. The tissues of the gastrohepatic omentum are edematous. The heart is normal save for edema of the fibrous tissue at the base of two aortic segments accompanied by edema of the segment of the tricuspid valve on the opposite side of the interventricular septum. The thymus is dull red throughout; the adjacent substernal lymphatic nodes are enlarged and red and the tissue about them is edematous.

Microscopic examination shows well-marked edema of liver and pancreas. In many places hepatic cells have separated from one another so that they are no longer arranged in columns. The cells composing acini and islands of Langerhans of the pancreas are similarly separated. The sinuses of lymphatic nodes in the positions which have been mentioned contain fibrin in abundance. Here, fibrin often radiates from the surface of necrotic cells.

In the following experiments no large lymphatic nodes escaped the operation planned for their removal, and edema of the liver and gall-bladder failed to occur.

Experiment VIII. Dog, weighing 8000 grams. The operation previously described was repeated. On the twenty-second day after operation, the animal which had gained 1200 grams in weight received cantharidin, 0.013 gram; 870 c.c. of urine passed during the following day contained 4.61 grams of sugar. Cantharidin, 0.006 gram, on the twenty-fifth day caused no glycosuria. Death followed within fifteen hours the administration of cantharidin, 0.02 gram; 925 c.c. of urine contained fairly abundant albumin but no sugar.

Autopsy. Liver is deep red; there is no edema of the gall-bladder. Above the splenic arm of the pancreas is a small lymphatic node 0.3 by 0.5 cm. The pancreas is slightly edematous and there is well-marked edema of the gastrohepatic omentum in the neighborhood of the lesser curvature of the stomach. Microscopic examination of the liver shows congestion but no edema.

Experiment IX. Dog, weighing 6000 grams. The regional hepatic nodes together with other abdominal lymphatic nodes were removed. Cantharidin, 0.013 gram, administered on the eighteenth day caused death after forty hours; urine, 820 c.c., collected during the following day contained abundant albumin and 8.04 grams of sugar (Benedict's method; fermentation not tested), and on the next day the urine (80 c.c.) contained a moderate amount of albumin and 0.18 gram of sugar (fermentation not tested).

Autopsy. The liver is pale brown red; there is no edema of the gall-bladder. Dilated lymphatics pass from liver and uniting form a large trunk which passes into the retroperitoneal tissue and joins the receptaculum chyli. No lymphatic nodes are found at the base of the duodenal mesentery nor along the superior margin of the splenic arm of the pancreas. Microscopic examination shows no edema of the liver or of the pancreas.

The experiments are inconclusive with regard to the effect of the removal of lymphatic nodes upon the action of cantharidin.

When, on the one hand, some of the regional nodes escape operative removal (Experiment VII) these nodes under the influence of cantharidin may oppose obstruction to the flow of lymph and in consequence edema occurs. When, on the other hand, all nodes are removed, collateral circulation (Experiment IX) may permit the lymph to flow into the thoracic duct and no edema follows administration of cantharidin. Although the number of experiments is too small to define the action of cantharidin in animals deprived of regional hepatic lymphatic nodes, they support the view that occlusion of lymphatic channels, in association with increased lymph formation, is the cause of the edema which follows administration of cantharidin.

The foregoing experiments define the changes which accompany edema of the liver and of the gall-bladder. Separation of columns of liver cells from adjacent capillaries, the intervening space containing serum and often red blood corpuscles, and separation of liver cells from one another are manifestations of edema of the liver.

The flow of lymph from the thoracic duct is profoundly modified by cantharidin; after administration of the drug the flow diminishes or ceases completely. Coincident with cessation and within three hours after administration of the poison edema of the liver and gall-bladder may be well advanced. Edema caused by cantharidin is almost wholly limited to these organs and to the adjacent lymphatic nodes.

Edema of the liver is dependent upon changes in the lymphatics and in the lymph sinuses of the regional lymphatic nodes, the effective change being the formation of fibrinous coagulum within the sinuses. Such coagulum often has its origin about cells injured by the poison, shreds of fibrin radiating from partially or completely necrotic cells.

Obstruction interposed by fibrin formation within lymphatic nodes is overcome in a certain number of experiments and diminished flow from the thoracic duct is followed by an output which may considerably exceed that observed before administration of the poison. Distention of lymphatics in the liver and occurrence of

edema during the period of diminished flow indicates that increased formation of lymph occurs in the liver before increased flow of thoracic lymph demonstrates its presence. In one experiment increased flow was not preceded by a period of diminished output; obstruction to outflow from lymphatics failed to occur or was insufficient to diminish the flow of lymph below normal. In this experiment edema of the liver and gall-bladder was absent.

A poison which is capable of causing nephritis increases the flow of lymph from the thoracic duct; it acts as a lymphagogue. In the presence of some additional factor, such as obstruction within the regional lymphatic nodes, edema results. These changes are coincident with the production of the renal lesion and are not the result of disturbance of renal function. They furnish by analogy support to the view that dropsy in association with nephritis is caused by the action of an irritant which simultaneously injures the kidney and increases the permeability of vessel walls elsewhere in the body.

DISCUSSION

Dr. S. J. Meltzer: What influence does cantharidin have upon the bloodvessels of the portal circulation besides the permeability? Could it not be possible that it causes constriction of the bloodvessels of the liver?

Dr. J. George Adami: I am glad that Dr. Opie has taken up the study of hepatic edema. From my own postmortem observations I am convinced that the condition is far from uncommon; but there is curiously little regarding it in literature. If I remember aright, the only general article in which it receives adequate reference is that by C. Sternberg in the second volume of Aschoff's *Pathologische Anatomie*. The histological picture is very characteristic, with a widespread zone separating the endothelium of the synosides from the underlying liver cells. Since 1894, when I found the condition very pronounced in the livers of cattle suffering from so-called Pictou cattle disease, employing pipettes for routine bacteriological cultures from the livers at autopsies, I have been impressed by the frequency with which in place of pure blood there is sucked into the pipette a much diluted blood which can only indicate relatively abundant lymph in the organ, or, in other words, an edematous condition.

Dr. Eugene L. Opie: I have made no study of the changes in the bloodvessels of the liver. The occurrence of edema during the first two to three hours of the experiment at a time when flow of lymph from the thoracic duct has almost ceased, together with the exceptional experiments in which there has been no diminution of blood flow and an absence of edema, have suggested that the retardation of lymph flow is the result of obstruction to the flow through the lymphatics rather than to a lack of lymph formation as the result of constriction of bloodvessels.

SOME CLINICAL OBSERVATIONS ON THE DRUG TREATMENT OF EDEMA

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In the following observations no attempt has been made to carry out extensive comparative experimental studies, regarding the action of the various agents in the treatment of edema, but rather to select a few drugs and determine, if possible, their value in different types and stages of edema. Also to note whether the failure of the individual to react to diuretics has any prognostic value.

The field of experimental therapeutics has recently furnished some interesting information upon the effect of diuretics in experimental nephritis. Animals with a mild type of nephritis respond in a normal manner to diuretics, the renal vessels dilate, and there is an increased flow of urine. When, however, the renal changes are so extensive as to render the animal aneuric all diuretics fail to act. Coincident with the appearance of edema in all experimental nephritis, the renal vessels either lose their power to dilate in a normal manner, after caffein, digitalis, or sodium chloride, or in case they respond in a normal manner by dilating no diuresis results. In other words, when the kidney in nephritis reaches the point where it is unable to eliminate water, it has lost its power to respond to diuretics. This is in accord with clinical experience, as in severe cases of nephritis efforts to excite diuresis are usually futile.

Two types of cases were especially observed: renal edema due to acute or chronic nephritis and edema, chiefly cardiac in origin, in chronic interstitial nephritis. In this latter group of cases there was, as a rule, high blood pressure, and these patients suffered from dyspnea, so that the effect of treatment upon this symptom would be observed. With three exceptions the patients were hospital

cases, selected because they had proved refractory to the ordinary treatment, as alkaline, diuretics, caffein, sweats, catharsis, salt-free diet, and restricted liquid intake. All these patients had been in bed for a week or more so that the effect of rest could be eliminated.

The diuretics selected were digitalis, strophanthin intravenously, theophyllin, and Fisher's solution. This latter solution was prepared by using 8 grams of crystalline sodium bicarbonate and 15 grams of sodium chloride to a liter of water.

Chronic Interstitial Nephritis. It is generally considered that broken compensation due to high blood pressure is one of the most unsatisfactory cardiac conditions for treatment, as it is extremely difficult to even temporarily restore compensation under such adverse conditions. A group of 8 cases of this character were given digitalis, either in the form of a tincture or digipuratum by mouth, and in 1 case, digipuratum intramuscularly. In only 1 of these 8 was there a marked diuresis; this patient received daily the digipuratum intramuscularly and reacted by a moderate increased output of urine. The average daily output of urine for three days preceding the use of the digipuratum was 860 c.c., and for the three days following its use 1400 c.c. The maximum diuresis occurred during the first twenty-four hours, when it reached 1700 c.c., gradually diminishing until on the third day it was only 1200 c.c. With this exception the maximum daily increase in the other patients did not exceed 200 c.c., and in the majority of cases no diuresis occurred, or it was so slight as to be questionable. In some of these patients, however, the dyspnea was considerably relieved, although there was no change in the urinary output. With a single exception all of these patients tolerated the digitalis well; one developed a marked bradycardia after even minute doses (0.08 grams daily) of digipuratum.

It was the above group of cases that showed the most striking effects following the use of theophyllin. This was administered in capsules in doses of 0.25 grams daily. On account of the nausea which usually developed it was rarely that the drug could be continued more than three days. After a respite of a few days the theophyllin could again be given, and by this intermittent form of treatment the edema would largely disappear. In this group of 10

cases where theophyllin was tried 7 had previously received digitalis, with very slight if any effect upon the edema. All of this group had interstitial nephritis with edema of the cardiac type. One patient in uremic coma had very slight edema, and was the only case in this series that failed completely to react to theophyllin. The patient died two or three days after entering the hospital. Diuresis was marked within twelve to eighteen hours after the first dose of theophyllin, reached its maximum as a rule within forty-eight hours, and continued until the drug was stopped on account of nausea or until the edema had largely disappeared. In the few cases where it was given continuously for a week or more, the daily output of urine grew gradually less after the first forty-eight hours, until at the end of the week, when the edema had practically disappeared, the daily output was only slightly in excess of that passed previous to the administration of the theophyllin. As an example, a patient who had been passing on an average of 750 c.c. daily, had the following daily output for the six days he received the theophyllin: 1720, 2070, 2420, 1200, 1000, and 800 c.c. The average daily output of urine in the 9 cases before receiving the theophyllin was 644 c.c., and the daily average for two days following its use was 2105 c.c. The minimum diuresis was an increase from 610 to 1360 c.c.; the maximum from 630 to 3530 c.c. As a result of the lessened edema, the patient was more comfortable, although when marked dyspnea was present this was only moderately relieved. In this respect the beneficial results were much less striking than with digitalis or strophanthin. Apparently the theophyllin had very slight beneficial effect on the heart, but acted chiefly upon the renal circulation.

During the last few months we have injected strophanthin intravenously in thirty patients, and several of these have received repeated injections. From this number 10 cases were selected where the patient suffered from cardiac incompensation, secondary to a chronic nephritis. All of these patients were decidedly dyspneic and had more or less extensive edema. After a single intravenous injection of $\frac{3}{4}$ mg. there was only a very moderate diuresis. This continued, however, for several days, the edema gradually growing less. The dyspnea was, however, very much lessened, and in this respect the action was much more satisfactory

than after the use of theophyllin. Most striking was the very frequent prolonged relief after a single injection. When decided improvement was noted after a single dose it was rarely necessary to repeat the drug until five or six days had elapsed. In several instances, by repeating the injection about once a week, the patient was kept reasonably comfortable, when other forms of treatment, as sweats, laxatives, and digitalis, had failed to give even temporary relief. When the strophanthin was injected slowly there was, as a rule, a moderate increase in blood pressure, which in none of the cases tested exceeded 20 mm. of mercury. One patient with a very marked cyanosis had a drop of 20 mm. in the blood pressure following the injection, no doubt due to the effect on the vasomotor centre of the improved oxygenation of the blood. As a rule, no improvement was noted in the patient's condition until after a lapse of one or two hours. The intravenous injection was not followed by serious consequences except in one instance, and that in a patient with a double mitral lesion, and not included in the above series. The cases had been very resistant to all forms of treatment, gradually growing worse, when as a last resort strophanthin was injected very slowly into the vein. The patient died about twenty minutes later, and apparently the strophanthin hastened the fatal termination.

Acute or Chronic Parenchymatous Nephritis. Five patients with marked renal edema due to acute or chronic parenchymatous nephritis were observed. Four of these patients had what is classed clinically as an acute exacerbation of a chronic parenchymatous nephritis; the other patient had an acute nephritis with blood pressure of 160 mm. In three of these patients, theophyllin failed to excite any diuresis, even after it had been continued several days. Apparently when diuresis fails to appear within forty-eight hours it is futile to continue the theophyllin. The other two patients reacted by an increased urinary output, in one case from 350 to 1740 c.c., in the other from 900 to 1600 c.c. Four of these five patients died within two weeks from the time the test was made; one, the acute nephritis, showed marked improvement, is still living quite comfortably and almost free from edema. This patient always reacted well to the theophyllin. One patient who on the beginning reacted quite well to theophyllin later failed to respond, and died in

uremia. It would appear from these few observations that failure of the kidney to react to a diuretic like theophyllin indicates a grave disturbance. Digitalis, strophanthin, and alkaline diuretics were tried in each of these patients, but without any effect. Even in the two patients where theophyllin excited diuresis this was very moderate in degree as compared to that observed in the cases of cardiac edema associated with interstitial nephritis.

Four of the patients in the above group were given Fisher's solution, prepared by dissolving 8 grams of crystalline sodium carbonate and 15 grams of sodium chloride in 1 liter of water. Two of the patients received the solution per rectum, the other two by intravenous injection. Theophyllin had previously been tried in each of these cases and in only one was there any effect. The two patients taking the solution per rectum received 400 c.c. every six hours, and this was continued for two days. They had been passing from 300 to 400 c.c. daily, and there was no appreciable increase during or after the treatment, or any improvement in their conditions. Two patients were given 1000 c.c. of the solution intravenously. One of those patients had been passing on an average of 350 c.c. of urine daily. During the twenty-four hours following the injection he passed 1120 c.c., the day following 680 c.c., and then the previous daily output. The patient passed in the two days 1800 c.c. Previous to the treatment he had passed during the same period 700 c.c., he received in the injection 1000 c.c., so that he only passed slightly more than the unusual amount plus the quantity injected. There was no apparent improvement in the patient's condition. The second patient receiving the intravenous injection reacted in the same manner—the patient passing during the twenty-four hours slightly more fluid than had been introduced.

In addition to these 4 cases, Dr. Cornell at the Cook County Hospital kindly furnished me with the data of 4 cases where Fisher's solution was used, but the daily output of urine not measured, depending upon inspections to determine the effect on edema. During the treatment the urine of these cases was examined microscopically. The patients each received 2000 c.c. daily per rectum by the drop method for three days. Three of the patients had parenchymatous nephritis, with marked edema, and in each instance, in

addition to the casts, blood in the urine. In none of these cases was there any appreciable change in the edema. The amount of blood in the urine was, however, distinctly lessened. The fourth patient had apparently an interstitial nephritis, cardiac asthma, scant urine, and very slight edema. After the Fisher solution had been given for two days the edema became so marked that it was necessary to discontinue its use.

These observations do not add anything to our knowledge of nephritis, but merely emphasize certain well established facts. When the permeability of the kidney to fluids in nephritis is seriously impaired it is difficult and often impossible to restore this function by any measures at our command. Edema of cardiac origin, even when secondary to nephritis, may often be at least temporarily relieved by diuretics or cardiac tonics.

DISCUSSION

Dr. H. A. Hare: The remarks which have just been made in regard to diuretics in renal disease support the idea that you cannot have secretion if you have not got a glandular tissue that will carry it out. If the secreting tissue is gone I do not see how we can expect any drug treatment, digitalis or theocin, to produce any effect. The more I study the influence of various diuretic drugs upon the urinary flow the more convinced I am that we must at the same time influence the hepatic function. I believe there is a relation between the liver and the kidney which is much closer than we think at the present time. Where our diuretics fail and there is some healthy secreting epithelium the relief of hepatic engorgement usually results in increased flow of urine. Whether this is due to the fact that some changes take place in regard to the formation of urea and the urea acts as a diuretic I do not know. One point is that it is of little value to make the patient pass a large quantity of fluid unless at the same time we can increase the output of solids. A much more efficient way is by purgation or tapping, and because if the patient is unable to get rid of solids the mere passage of an increased quantity of urine from his kidney is not of very great value to him. In regard to the use of theocin, and the statement that no deleterious effect was had therefrom, it is not a very poisonous substance, but there are a number of cases on record in which administered by the mouth or hypodermically it has produced death.

Dr. F. P. Kinnicutt: My own clinical experience is entirely corroborative of Dr. Miller's observations on the comparative effect of digitalis, strophanthin, and theocin. In other words, our experience in the use of digitalis and strophanthin in this group of cases has been well marked relief in dyspnea, but no increased diuresis. On the contrary, with theocin we obtain increased diuresis, but without improvement of the dyspnea.

Dr. Theodore C. Janeway: Dr. Miller's careful observation on these drugs ought to bring home to us the very great importance of the investigations of kidney function which are being carried on both in regard to water and salt excretion and the excretion of special test substances. If we could get to the point where we could discriminate in the group of edemas, those due to definite loss of a particular secreting function, it would go very far to simplify the treatment of these patients. As physicians I think we are at a disadvantage in judging the success of any method of treatment, in that we cannot, as the surgeons do, always separate the inoperable cases in our statistics and leave only the operable cases with such a percentage of cures. We often deal with patients whose lesions are so advanced as to make cure impossible, and yet we are unable to separate these cases in our criticism of our experience, and they tend to complicate the situation. They are medically the analogue of the surgeon's inoperable cases. The problem of the water and salt management of edematous cases is a matter of vast importance and complexity. I have seen cases where the response to salt restriction was admirable, but where continued salt restriction did harm, once you freed the patient from edema, and it became necessary to again increase salt. Water is the best diuretic if the patient can excrete water. There may come a point where one holds back water too long. These decisions can only be made by experiment in each case under careful control by laboratory study. In regard to dropsy of the serous sacs, in one case I observed we were able to free the patient from subcutaneous edema completely, and take off twenty pounds without any increase in the NaCl output by the urine. We did it by salt restriction and tapping the chest frequently. The salt excess regularly came out in the pleural effusion and the subcutaneous edema disappeared.

Dr. E. Libman: When the agents discussed by Dr. Miller do not cause diuresis I am accustomed to try some of the older diuretics, and often a striking result is obtained. I remember a case treated by Dr. J. Rudisch ten years ago with oil of juniper, a drug that must be used with great caution. The patient was water-logged for months, and all the ordinary diuretics had been used. The juniper caused so marked a diuresis that the edema entirely disappeared, and the patient was doing well when seen several months later.

In several cases, I have seen splendid results from the use of the infusion of apocynum. I usually give it by rectum, diluted with water. I should like to ask Dr. Miller whether he has tried the various remedies in conjunction with the Karrell diet.

Dr. S. J. Meltzer: Dr. Miller has brought out a fact on the selective action of drugs worth noting. Caffein and digitalis are stimulants for the heart, but caffein causes dilatation of the bloodvessels of the kidney, while the vasodilating effect of digitalis is only slight. It would be very rational for physicians to give digitalis and caffein together in such cases.

Dr. S. Solis Cohen: Following the hint that Dr. Janeway has given about inoperable—better, perhaps, to say *immedicable*—cases, I shall speak only of those in which the kidney and heart are capable of responding to drugs. There is a drug which in my own hands has been quite satisfactory in association with or substitution for digitalis, and that is spartein. Its action is not precisely the same as that of digitalis. Rather does it reduce abnormal blood pressure, by enlarging the volume of the peripheral arteries; and it markedly increases the output of urinary water and solids. It is also the well-known empirical practice of physicians in general to associate with digitalis as a diuretic one of the vegetable-acid salts, preferably potassium acetate or citrate; much better results being thus obtained than when either drug is used singly. The observations cited may partially explain the reason. Clinically I have found it of considerable advantage to rotate in the use of these drugs, using caffein, digitalis, strophanthus, spartein, etc., either in alternation or on successive days, or for successive periods. Sometimes the association of two is better than the use of one alone.

Dr. D. L. Edsall: I should like to ask Dr. Miller if he has seen any positive bad results from theocin? It is, perhaps, the strongest stimulant we have to the renal secretion. I have been rather strongly inclined to believe that in some cases it may cause the appearance of an increase in the amount of albumin and casts. Does Dr. Miller find that correct?

Dr. Miller: In regard to Dr. Libman's questions, I have not used the Karrel diet in conjunction with digitalis, nor have I used spartein. I have never seen any bad results following the use of theophyllin except nausea. For this reason it is rarely advised to administer it for more than two or three days consecutively. I have never been able to detect any injury to the kidney after its use, as shown by the microscopic examination of the urine. Fisher's solution, to which I referred in my paper, consists of 8 grams of sodium carbonate and 15 grams of sodium chloride to the liter.

COMPLETE AND PERMANENT HEART-BLOCK FOLLOWING THE USE OF DIGITALIS IN AURICULAR FIBRILLATION

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One of the commonest, as well as one of the most interesting, varieties of cardiac irregularity is that known as auricular fibrillation. In this condition the auricles, instead of contracting rhythmically, are thrown into a state of tremulousness involving small bundles of fibrils.

"The walls of the auricle stand in the diastolic position; systole, either complete or partial, is never accomplished; the wall, as a whole, is stationary, but careful examination of the muscle reveals an extremely active condition; it appears to be alive with movement; rapid, minute, and constant twitchings of undulatory movements are observed in a multitude of small areas upon its surface" (Lewis).

The result, usually, is a rapid and extremely irregular pulse. From the turmoil in the auricles a shower of impulses passes down the bundle of His into the ventricles. The weakest of these impulses fail to affect the ventricles. The stronger ones, occurring at irregular intervals, cause ventricular systole and lead to the production of what used to be known as the pulsus irregularis perpetuus (Hering) or arrhythmia perpetua (Gerhardt). These terms are not accurate, since the condition is occasionally compatible, with a regular pulse and, while usually permanent, may be transient (Mackenzie, Hewlett and Barringer, Fox and others).

The venous pulse, in these cases, is characteristic, and from it the diagnosis can readily be made. The *a* wave disappears entirely

from the jugular sphygmogram, and the same is true of the esophageal tracing (Hewlett) and the electrocardiogram (Hering). Whenever the diastole is somewhat prolonged a series of fine wavelets may often be seen in the venous sphygmogram (Figs. 5 and 6). Mackenzie was at first inclined to consider these as artefacts, but since they correspond in their rate with similar waves in the electrocardiogram, he now agrees with most other observers that there is reason to suppose them an expression of the auricular tremor.

While in most cases of auricular fibrillation the pulse is rapid and irregular, it need be neither. In his classical monograph on *Nodal Bradycardia*, Mackenzie has reported a considerable number of cases of this sort, in some of which the pulse was slow and irregular, in some slow and regular. Gibson, Lewis, and others have reported similar cases. A seductive theory, in explanation of this phenomenon, has been advanced by Lewis. He considers the occurrence of a slow pulse in auricular fibrillation to be an expression of an impaired conductivity on the part of the auriculoventricular bundle. If the heart-block is partial, an occasional tremor only goes through and causes ventricular systole. The result is a slow and irregular pulse, sometimes with long pauses. If the block is complete, the fibrillating auricles can no longer affect the ventricles. The latter establish their own rhythm and beat slowly and regularly as in an ordinary case of complete heart-block. From the nature of the case the validity of this explanation cannot be established in every instance. But, as Lewis has pointed out, one at least of Mackenzie's cases strongly supports this view. The patient, a subject of rheumatic fever, was known to have had impairment of conductivity, in greater or lesser degree, for twelve years. He then suddenly developed slow and irregular action of the heart, with evidence of auricular fibrillation. This lasted a week, at the end of which time both auricles and ventricles again resumed their rhythmic action, but with an *a–v* interval twice as long as normal. Several months later the slow and irregular pulse, with auricular fibrillation, returned and thereafter persisted. Gibson has reported an equally instructive case. The first tracings obtained were those of ordinary partial heart-block, with an auricular rate of 168 and a ventricular of 42. On one occasion auricular fibrillation set in,

with an irregular but still phenomenally slow pulse. A post-mortem revealed an increase in the fibrous tissue of the *a–v* bundle with wide separation of the fibers consisting it. Lewis and Mack have reported a case of auricular fibrillation in which the ventricles beat regularly at a rate of 30 per minute. By means of the electrocardiograph they showed that the impulses from the fibrillating auricles were not transmitted to the ventricles and that the impulses originating the rhythm of the latter started at a point in the ventricular wall not far removed from the auriculoventricular ring. There is thus good reason to suppose that the slow pulse occasionally seen in auricular fibrillation is due to partial or complete heart-block, as the case may be.

Mackenzie has shown that digitalis slows the pulse far more readily and to a far greater extent in auricular fibrillation than in any other cardiac condition, with the exception of cases of partial heart-block. This phenomenon can readily be observed by anyone who studies this condition. Lewis was the first to suggest the theory that here too the slowing produced by the administration of digitalis is due to the production by this drug of a partial or complete heart-block, thus preventing the passage of some or all of the fibrillation impulses at the *a–v* junction.

It is well known that digitalis, either through the vagus or directly, or both, often depresses the conductivity of the bundle of His. This is especially the case where the conductivity of the bundle has already been impaired by some organic lesion. Thus cases of partial heart-block are nearly always aggravated by digitalis, and the case of Windle, in which heart-block was apparently produced *de novo* by the administration of digitalis, was one of rheumatic mitral disease, in which an impairment of the conductivity of the bundle is not infrequently found. Similarly Mackenzie has shown that of cases of auricular fibrillation those which are of rheumatic origin or those in which mitral stenosis is present are most susceptible to digitalis. It is therefore reasonable to suppose that in these cases we have, besides the auricular fibrillation, a preëxisting impairment of conductivity, and that digitalis here produces its exceptionally great retardation of the pulse by still further depressing the conductivity of the already organically diseased bundle. Further

clinical and, if possible, experimental evidence is needed to prove the validity of this theory in all cases. It is believed that the second case, to be reported below, may be of value in this connection.

In all cases hitherto reported in which digitalis has slowed the pulse in auricular fibrillation the action of the drug has been temporary. Even when the slow regular pulse of complete heart-block has been produced a discontinuance of the drug has been followed by a return of the rapid, irregular pulse characteristic of uninfluenced auricular fibrillation. That this need not always be the case it is the object of this communication to show. It would seem from the two cases to be related below, that occasionally the depression produced by digitalis in the conductivity of the diseased bundle may result in a permanent injury to the latter, leading to the production of a complete and permanent heart-block with its characteristic regular and extremely slow pulse. They further seem to show that this is an eminently undesirable accident, since in both patients the condition after the establishment of the complete block was far worse than before, and death ensued in ten and sixty-four days respectively.

Case I.—Male, aged eighty years. No rheumatism, syphilis, or alcoholism. In 1868, while suffering from a severe laryngitis, he had a sudden attack of syncope, and thought he was dying. He felt well the next day, but soon after began to have periods of dyspnea on slight exertion, which slowly grew more frequent and more severe. He did not consult a physician, but twenty years later they had become so harassing, coming on once a month or oftener and lasting several days, that he retired from business. Since 1906 he had been more or less of an invalid—weak, dyspneic, with periods of cardiac palpitation and occasional precordial pain. His feet and legs became edematous and continued so until I saw him in 1908. I found him with an enormously dilated heart, mitral and aortic regurgitation, marked arteriosclerosis, congested and ptotic liver, great edema of legs, rapid and irregular pulse, urine scanty, with albumin and casts. The usual treatment led to a gradual amelioration of his symptoms. Every few months thereafter he had a relapse, which always yielded promptly to digitalis.

In April, 1910, I began to study his pulse with the Jaquet cardiosphygmograph, which showed the condition to be one of auricular fibrillation. On June 21, having been without medication for some time, his pulse was

irregular, averaging 70 beats per minute, with occasional bigeminy and with the jugular pulse of auricular fibrillation (Fig. 1). Under digitalis (digalen, 1 c.c., t. i. d.) his pulse became slow (38 per minute) and nearly regular (Fig. 2), without subjective improvement. The digitalis was discontinued, but the heart-block pulse persisted (Fig. 3), dropping to 33 beats per minute on July 5, and continuing unchanged until his sudden death on July 8. An autopsy was refused.

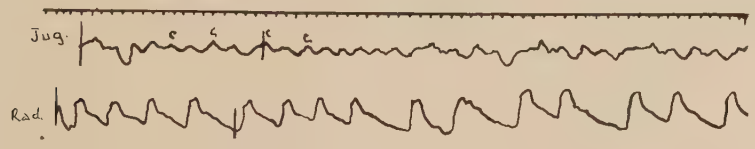

FIG. 1.—Case I. C. S., June 21, 1910. Jugular and radial pulse, showing auricular fibrillation uninfluenced by digitalis.

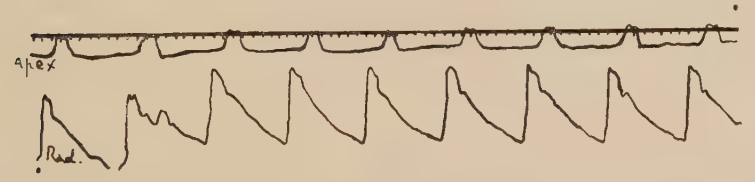

FIG. 2.—Case I. C. S., June 28, 1910. Apex beat and radial pulse after a week of digitalis. Note typical heart-block pulse. The irregularity in the second pulse beat is due to a movement of the patient's hand.

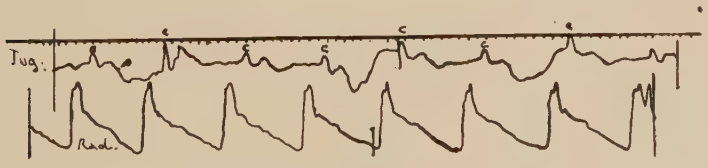

FIG. 3.—Case I. C. S., July 5, 1910. Jugular and radial tracing, one week after digitalis was discontinued. The jugular pulse shows auricular fibrillation, the radial complete heart-block.

We have here, then, a case of auricular fibrillation in which a moderate dose of digitalis produced complete auriculoventricular block, the latter persisting until the patient died, ten days after the discontinuance of the digitalis.

CASE II. —Male, aged fifty-eight years, was admitted to the Washington University Hospital, service of Dr. George Dock, on December 8, 1911. Besides the usual diseases of childhood he had had pneumonia at the age of twenty-eight years and meningitis at forty-nine years. There was no history of rheumatism or of syphilis, but a definite one of long-continued alcoholism. In June, 1910, he was severely injured about the head. The

accident was followed by a series of convulsions, suggestive of epilepsy, and recurring at irregular intervals up to the time of his death. nearly two years later. During some of these he bit his tongue and otherwise injured himself. In October, 1910, he first noticed evidence of cardiac incompetence: dyspnea and cardiac palpitation, varying in intensity, but on the whole growing steadily worse until he entered the hospital on December 8, 1911. At this time the heart was found moderately enlarged, with evidence of dilatation of the left auricle and irregular in its action. A low-pitched murmur was audible over the apex, beginning just after the second sound and accompanying the first portion of diastole. When the latter was long a distinct interval of silence could be made out between the end of the murmur and the beginning of the first sound. There was some pulmonary edema but none of the feet. The liver was not enlarged. The maximal blood pressure varied from 110 to 140 mm. Hg. according to the strength of the individual cardiac contractions, the minimal pressure being about 90 mm. The jugular and radial tracings showed the presence of auricular fibrillation (Fig. 4), confirming the evidence of the murmur, which was identical with that described by Mackenzie as characteristic of mitral stenosis when coexisting with auricular fibrillation.

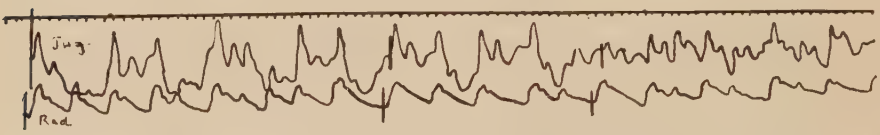

FIG. 4.—Case II. J. N., December 16, 1911. Jugular and radial pulse uninfluenced by digitalis. Auricular fibrillation.

Digitalis was given, at first tentatively, but later, when this seemed ineffective, in doses of 1 c.c. of the tincture every four hours. No marked effect was produced until eight doses had been given. Then at midnight the resident, Dr. Brotherhood was called, as the patient was in convulsions. He found the pulse 40 beats per minute, with long periods of asystole, and ordered the digitalis discontinued. The next day the patient seemed weak, but was not carefully observed. On the following day, however, he went from one convulsion into another, each lasting a minute or two, apparently accompanied by hallucinations, and followed by a brief period of confusion. There was no dyspnea or cyanosis. The pulse was very slow but strong, with frequent intermissions, sometimes lasting several seconds, and very suggestive of heart-block (Fig. 5, 6, and 7). It sometimes seemed as though a seizure were preceded by an unusually long intermission, but of this I was not quite sure. It was impossible to feel or record the pulse during an attack on account of the violence of his motions. The cardiac outlines and sounds did not differ from those previously recorded. Atropine sulphate, gr. $\frac{1}{60}$

hypodermically, produced no effect upon the pulse. This same day (December 20) the patient was taken home, where I saw him thereafter at frequent intervals. On December 20 the pulse was nearly regular, 20 beats per minute, still with the jugular pulse of auricular fibrillation (Fig. 8). On the following day the pulse became entirely regular, and from this time until his death on February 23 the cardiac condition was unchanged.

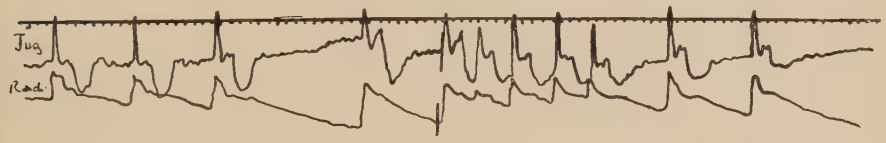

FIG. 5.—Case II. J. N., December 20, 1911.

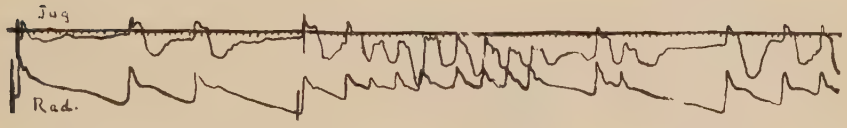

FIG. 6.—Case II. J. N., December 20, 1911.

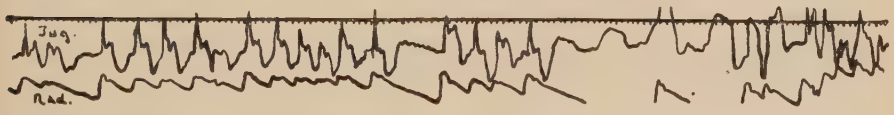

FIG. 7.—Case II. J. N., December 20, 1911. Figs. 5, 6, and 7. Jugular and radial pulse, twenty-four hours after digitalis was discontinued. Auricular fibrillation. The occasional long pauses between beats are suggestive of partial heart-block. In Fig. 7 two respirations are recorded in the jugular pulse during a period of asystole. During this and the following diastole the blood-pressure fell so greatly that the collapsing radial allowed the writing point to leave the paper.

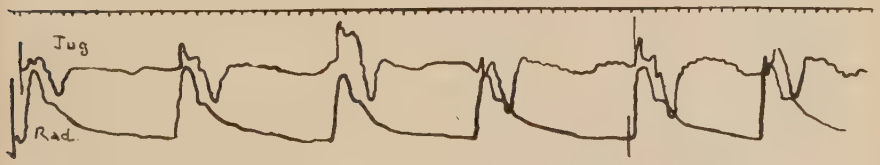

FIG. 8.—Case II. J. N., December 21, 1911. The pulse has become comparatively regular and very slow, suggesting nearly complete heart-block. As in all the tracings, the jugular pulse shows that the auricle is fibrillating.

The pulse remained very slow, varying between 30 and 40 beats per minute, entirely regular except for rare extrasystoles; many tracings were taken from time to time, of which two are here reproduced (Figs. 9 and 10). The cardiac dulness and the murmur remained unchanged. From week

to week the dyspnea increased, but there never was any evident cyanosis. The convulsions came on frequently and at irregular intervals, the latter sometimes being a week or more in duration. No difference in the pulse could be noted between the convulsive and non-convulsive periods. Frequent attempts were made to influence the pulse by swallowing, pressure on the vagi, large doses of atropine and of digitalis, but no effect could ever

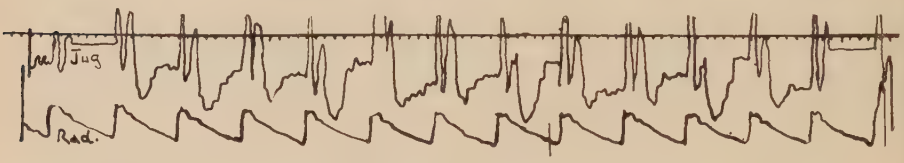

FIG. 9.—Case II. J. N., January 15, 1912.

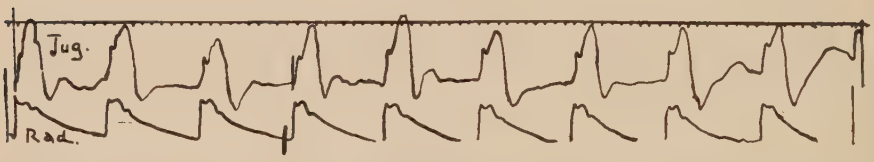

FIG. 10. Case II. J. N., February 16, 1912. Figs. 9 and 10. Two examples of nearly daily tracings taken between the onset of complete heart-block on December 21, and exitus on February 23. All show continued auricular fibrillation in the jugular pulse and evidence of complete heart-block in the radial.

be noted. The blood pressure remained of the heart-block type, the maximal pressure averaging 195 mm. Hg., the minimal 60 mm. On February 23 he died, with no change in his condition except a progressive weakness and dyspnea. Until a minute or two before his death, that is, as long as the pulse could be felt, it maintained its slow, regular rhythm. An autopsy was performed a few hours after death by Dr. George M. Smith, of the pathologic department of Washington University.

The following is an abstract of the pathologic findings, a more detailed account of which will appear elsewhere.

Anatomical Diagnosis. Valvular disease of the heart; mitral stenosis; fibrous myocarditis. General arterial sclerosis; calcification of part of ventricular septum, causing destruction of auriculoventricular bundle; edema of lungs, chronic pleuritis (right); chronic passive congestion of lungs, liver, spleen and kidney; ascites; porencephalus.

Two small cysts, probably caused by old hemorrhages, were

found at the base of the occipital lobes. Brain otherwise was normal. Sections from the cortex of the motor area showed no changes.

Weight of heart 317 grams. Moderate hypertrophy of both ventricles. Dilatation of both auricles. Thrombus was found in the wall of the left auricle. Both mitral leaflets were much thickened and produced a contraction of the mitral orifice so that this barely admitted the tip of the little finger. At the base of the aortic leaflet of the mitral valve there was a large irregular calcareous mass extending over into the ventricular septum. This nodule met and practically destroyed the auriculoventricular bundle just anterior to the septum membranaceum before the bifurcation of the bundle had occurred. The microscopic sections exhibiting the maximum point of injury showed that merely a few scattered muscle fibers still remained. The node of Keith and Flack contained a considerable amount of fibrous tissue.

This case presents several points of interest. Tracings 5, 6, and 7 seem clearly to show the onset of partial heart-block following the administration of digitalis. Tracing 8 shows evidence of nearly complete block on the following day. This, as indicated by tracings 9 and 10, became complete and remained permanent. The fact that neither vagal stimulation, atropine, or digitalis affected the block is evidence that the latter was not functional but organic, and this conclusion is borne out by the pathologic findings.

The conclusion thus seems justified that we had here a heart with an anatomically impaired auriculoventricular bundle, but one still competent to transmit auricular impulses; the digitalis, by still further depressing its conductivity, administered the *coup de grace* to the diseased bundle and led to its complete and permanent obliteration. It is possible, of course, that the block was entirely due to the gradual extension of the anatomic lesion of the *a–v* bundle, which at this moment happened to interrupt its continuity, at first nearly and then quite completely, independently of the digitalis, and that the administration of the latter was merely a coincidence. The fact, however, that the phenomenon followed the use of digitalis in two cases renders this hypothesis less probable than the other.

Whether the patient's convulsions were due to the bradycardia

remains problematic. Some of them were certainly epileptic, and perhaps all of them were. It may be that the cerebral anemia resulting from the block stimulated the brain to the production of an increased number of epileptic seizures.

It is a pleasant duty to thank my honored chief, Dr. George Dock, for permission to report this case, and for the interest shown during its study.

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DISCUSSION

Dr. H. A. Hare: It seems to me that the use of the polygraph, which has been so largely resorted to by Mackenzie, has shown definitely that much cardiotherapy is faulty unless we resort to this instrument. In regard to the use of digitalis, we should consider what we know in connection with its cardiac action. When digitalis stimulates the vagus it slows the heart by obstructing the impulse across His' bundle, although there may be some slight influence directly on the wall of the ventricle. If digitalis is given in partial heart-block there is very great danger of producing complete heart-block. On the contrary, where there is a complete heart-block, digitalis is a useful remedy. Where there is complete heart-block the digitalis results in speeding up the ventricle. So while in clinical medicine digitalis ordinarily slows the heart by influence on the vagus, if there is complete heart-block, digitalis speeds up the ventricle, and the ventricle, which has been beating only 40 or 50 a complete hour, will beat 70 or 80 times under the influence of digitalis. I have always supposed that this was the reason that in true auricular fibrillation digitalis

does good. Although a very careful perusal of Mackenzie's article has been made by me, I fail to find any expression of opinion as to why he gets his good results in this condition. In regard to atropine, it is interesting to note that in cases of cardiac disease with great irregularity, with abortive beats, within the last eighteen months I have gotten extraordinary results by dropping ordinary cardiac stimulants and using heroic doses of atropine. Those of us who have used atropine in the laboratory know that $\frac{1}{150}$ grain is not adequate to put out of activity the peripheral ends of the vagus. In a case which has just passed from my observation, a man who failed to be benefited as to his symptoms by cardiac tonics in all the different doses that could be possibly conceived of, materially improved when he received not less that $\frac{1}{100}$ grain in the twenty-four hours. The abortive beats ceased, the dyspnea disappeared, and in place of showing a radial pulse which was now present and now not the pulse became quite regular, and I believe that that was due to the fact that the atropine permitted the passage of impulses across His' bundle. I would suggest in these cases that large doses of atropine be given. There is another point of which I am sure. I have noticed it clinically. The patients suffer more if you give $\frac{1}{150}$ of atropine hypodermically than if you give a larger dose. The same is true of hyoscine. If you give a man as much as one-fifth of a grain in twenty-four hours, instead of complaining of dryness of the tongue the complaint is that they have too much spittle in the mouth instead of too little.

Dr. S. J. Meltzer: The case of Dr. Taussig has definite relation to the communication of Dr. Auer made before. Auer stated that toxic doses have the power of causing in rabbits a total or almost total loss of irritability of the heart ventricles. It is plausible to assume that in cases in which the conductivity was impaired the administration of digitalis finished up the irritability and in this way produced a complete heart block.

Dr. James Tyson: I wish to say a word to what Dr. Hare said of atropine in irregular heart. I have had very satisfactory results from it. To me it has been a valuable remedy and should substitute digitalis many times when the latter drug is given. I am inclined to think further knowledge will lead us to use less digitalis in the treatment of irregular heart.

Dr. L. F. Barker: Perhaps we can use digitalis and atropine together very well. Digitalis combines with the heart muscle directly and also combines with the vagus nerve; it is both myotropic and vagotropic. When we need digitalis we can give atropine with it and throw out the vagus influence while retaining the direct effect upon the heart muscle.

Dr. George Dock: I agree with Dr. Taussig's reserve. In regard to the use of digitalis in such cases it seems to me important to remember that if we are making proper examinations, including the use of the polygraph, digitalis is not only safe, but that observations so made are certain to bring an addition to our knowledge. If I am not mistaken about Dr. Mackenzie's work, it is still in the experimental stage in regard to the use of digitalis in such cases. I think he is not entirely satisfied with the present use of digitalis in auricular fibrillation, but his work is very carefully and systematically done and promises to get light on it. From the occurrence of heart-block in such a case one must not too quickly draw the conclusion that the patient has a complete lesion of the His bundle, and that ineradicable damage has been done by the digitalis. I do not agree with those who think that one can have symptoms of complete or severe disease of the His bundle without any disease at all. I reported a few years ago the case of a man in whom there were severe symptoms without complete degeneration, but with endarteritis of the vessel in one branch of the bundle. There were severe Stokes-Adams symptoms and permanent heart-block for two years. In connection with that case I never used atropine systematically, although I frequently experimented with it, and I believe there is a great deal in Dr. Hare's suggestion. I believe there is also some value in the use of strychnine. The man I mentioned with Stokes-Adams disease was able to do his work for two years with his pulse always below 30, and died suddenly one night while washing his hands. During that time he was always perfectly well, provided he was taking his $\frac{1}{20}$ grain of strychnine. If he went without it his pulse would intermit up to one-fourth of a minute.

Dr. Taussig: Dr. Hare's warning in regard to the use of digitalis in partial heart-block was entirely justified, but hardly applies to these cases with auricular fibrillation. In auricular fibrillation there is no way of telling whether a lesion of the bundle of His exists until after digitalis has been given. Then if the administration of digitalis is followed by a marked bradycardia, and if we subscribe to Lewis' hypothesis in explanation of this phenomenon, we may conclude that the conductivity of the auriculoventricular bundle is impaired.

Even in ordinary heart-block digitalis is sometimes indicated. Erlanger and Hirschfelder have shown that in such cases digitalis slows the auricle, thereby renders the block less complete and, as a result, speeds up the ventricle. In auricular fibrillation with auriculoventricular block, the digitalis cannot act in this manner, since it cannot produce any such effect upon the fibrillating auricles.

A STUDY OF THE CARDIAC LESIONS OF SUBACUTE BACTERIAL ENDOCARDITIS, WITH PARTICULAR REFERENCE TO HEALING OR HEALED LESIONS; WITH CLINICAL NOTES

By E. LIBMAN, M.D.,
NEW YORK

During the last ten years, I have had the opportunity of studying an unusually large number of cases of subacute bacterial endocarditis. Particularly in the last few years, I have become impressed with the great frequency of the condition (in 1911, I saw 27 cases). Altogether I have had the opportunity of studying at least 89 cases. Blood cultures were made in 75 of 78 active cases; by this I mean cases in which the causative bacteria were still present in the lesions at the time the patient succumbed. The other three cases were typical clinically. One passed out of observation, and the other two died. Autopsies were not obtainable.

Organisms were recovered from the blood of 73 of the 75 cultured cases. In 71 cases, the cocci characteristic of the disease were obtained,[1] and in 4 the influenza bacillus. The symptoms and lesions found in the latter group were practically the same as those found in the former, except that thus far the glomerular lesions which are found in the coccus cases were not seen in the kidneys of the influenzal cases that have come to postmortem examination.

I shall not now discuss the proper classification of the cocci found in this disease, leaving that for another publication. I shall simply say here that the cocci we have found seem to be identical with those found by other investigators. Until their exact status is determined we shall refer to them as the "endocarditis cocci" or "coccus." Studies by Rosenow indicate that the organisms are

derived from pneumococci, a view also discussed in the paper by Celler and the writer.

There were two supposedly active bacterial cases in which the blood cultures were negative. In the former five cultures were made in a variety of ways in our laboratory and one in another. All were negative. This patient died at another hospital and characteristic lesions were found in the heart with cocci in the vegetations. These cocci were not studied, but I have no hesitation in putting down the case as one belonging to the group of subacute bacterial endocarditis. In the other case two cultures were made, neither very satisfactory. This case died and there was no autopsy made. The clinical picture was, however, definite.

The term "subacute bacterial endocarditis" I have adopted instead of the older terms, "chronic ulcerative endocarditis," "chronic malignant endocarditis," "chronic infectious endocarditis," and "endocarditis lenta" (Schottmüller). I call all cases of endocarditis already proved to be due to bacteria (rheumatism is not so proved) "bacterial endocarditis," and divide the cases into "acute," "subacute," and "chronic" according to their clinical course. Many of the cases that belong in the group with which we are dealing last only four to six months, and are, therefore, certainly subacute and chronic. Some may prefer to apply the term "chronic" to cases that last over one year. When the infecting agent is determined in a given case, one substitutes its name for the word "bacterial." We thus speak of "acute streptococcus endocarditis," "subacute influenzal endocarditis," etc.

Besides the 77 active cases we have observed 11 cases which I believe belong in the group of subacute bacterial endocarditis, but in which the lesions found were in a healing or healed stage and in which the lesions were free from pathogenic bacteria. In 10 of the cases, blood cultures were made during life (in a few anaërobically), and no bacteria were found. In one case as many as nine cultures were made during a period of ten months, all with negative result.

There are many viewpoints from which such material as I have at my disposal could be presented. At this time I shall attempt to demonstrate that the lesions found in the cases of subacute bacterial endocarditis in which the mitral valve is involved are

characteristic. I hope to convince you that there are three stages in many cases of this disease, the bacterial, the bacteria-free healing, and the bacteria-free healed stage. I should also like to point out to you that at least some of the cases which we have been wont to call "chronic endocarditis with fever" are examples of the healed or healing forms of subacute bacterial endocarditis, for healing from a bacteriological or bacteriological and pathological standpoint does not necessarily mean recovery from a clinical standpoint.[2]

On this occasion I shall present my views as briefly as possible and refer to the literature in so far only as is essential. At another time I hope to cover the subject more fully and to discuss the lesions found in other forms of endocarditis.

I shall demonstrate for comparison some of the valvular lesions found in infections by the ordinary streptococci, pneumococci, staphylococci, and the gonococcus.

As you can easily see from my demonstration, when the mitral valve is involved in cases of subacute bacterial endocarditis (and it is involved in the larger number of cases) there is a tendency for the vegetations to spread up on the left posterior wall of the auricle, more than on the valve itself. Very often the chordæ tendineæ attached to the posterior flap are covered to a greater or lesser extent by vegetations. Nearly always the anterior flap is also involved and here the vegetations tend to grow down over the chordæ tendineæ, the involvement of the latter being often very extensive. Not uncommonly the chordæ tear, the torn ends at times being massed together by vegetations at the edge of the flap, or the lower ends may be found lying loose near the papillary muscles. The vegetations are yellowish, greenish, pinkish, or reddish in color, and vary much in size in different cases. As they grow older they become firmer and assume a more grayish color.

When the aortic valves are involved, the lesions are not usually characteristic and their extent is most variable. There may be only a small vegetation on one or more of the flaps of the valve. On the other hand, there may be enormous green masses that must block the orifice to a greater or lesser extent. The vegetations have a tendency to extend down over the endocardium at the position of the septum membranaceum and over the ventricular aspect of the

aortic flap of the mitral valve and down over the chordæ tendineæ. At times they have a stalactite-like appearance. There may develop an aneurysm of the aortic flap of the mitral valve. Ulceration of the aortic valve at times occurs; ulceration of the mitral flaps is rare.

A study of frequency of involvement of the valves, the left auricle, and the chordæ in the hearts from thirty-four cases of the disease in which the blood cultures were positive during life was made, with the following results:

	Cases.
Auricle, mitral valve, and chordæ	17
Auricle, mitral valve, chordæ, and aortic valve	5
Auricle and mitral valve	2
Mitral valve and chordæ	1
Aortic valve only	3
Aortic valve, chordæ, and aortic flap of mitral valve	4
Mitral valve, chordæ, and aortic valve	1
Auricle, mitral and aortic valves	1
Total	34

The auricle was involved 25 times, the mitral valve 27 times, the chordæ 28 times, and the aortic valve 9 times. The frequency of the involvement of the chordæ and auricle is very striking.

The lesions which we consider so characteristic of this group of cases we have not found in a large series of cases of acute endocarditis (58 in number) due to the streptococcus, pneumococcus, and the staphylococcus. In our own cases of acute gonococcus endocarditis we have not met with similar lesions. But I have, through the kindness of Drs. Asch and Humphries, of the German Hospital, seen one case of gonococcus endocarditis, apparently of only three weeks' duration, in which the lesions resembled those seen in the group of cases under discussion. The symptoms seen in the typical cases of subacute bacterial endocarditis were not present, nor were the characteristic glomerular lesions found in the kidneys.

And as, in the group of 34 cases just tabulated above, only one was due to the influenza bacillus and the other 33 to the endocarditis coccus, the lesions must be considered characteristic of infection by these cocci. There are occasional notes in the literature on such lesions in cases of bacterial endocarditis particularly by Osler[3] and Harbitz.[4] These will be discussed in the fuller paper to appear later.

After I had made these observations, I found (in 1909) lesions in a case in which a clinical diagnosis of chronic nephritis and uremia had been made, which appeared to me to represent the healed form of the lesions I had previously found in cases of infection by the endocarditis cocci. There were, as you see, extensive lesions on the wall of the auricle in a state of organization, and the chordæ tendineæ attached to the anterior flap were found torn, thickened, fibrous, and in part calcareous. Bacteria were not present. My opinion that these were the healed lesions of subacute bacterial endocarditis (in all probability due to the cocci) was confirmed recently by Dr. Baehr's[5] studies of the kidneys in all the material we have in the museum from cases of bacterial infection of the heart valves.

Dr. Baehr investigated particularly the glomerular lesions described by Loehlein[6] in cases of endocarditis due to the Streptococcus viridans of Schottmueller[7] which organism seems to correspond to the cocci found in our subacute cases. Dr. Baehr studied the kidneys of 27 cases of endocarditis due to the endocarditis coccus (Streptococcus viridans or Streptococcus mitis), which were still in the bacterial stage, and found the lesions described by Loehlein in 23. In 2 other cases, one an infection by the influenza bacillus and the other the case of gonococcus infection before mentioned (with rather acute course, but with endocardial lesions like those in the coccus cases), the lesions were absent.* In the kidneys of 54 cases of endocarditis due to the ordinary streptococci, staphylococci, the pneumococcus, and the gonococcus, no such lesions were found. The lesions must therefore be considered characteristic of infections of the heart valve by the endocarditis coccus.

In the kidneys of the case which I have just mentioned which I believed at the time the case came to post-mortem examination represented a spontaneously healed case (from the bacteriological and pathological standpoints) the characteristic glomerular lesions were found. After observing this case, I again looked over my collection of hearts from cases of subacute bacterial endocarditis and was surprised to find how often there is a tendency to healing

* Since Dr. Baehr wrote his paper, Dr. Thalheimer has studied with me the lesions in another subacute case due to the influenza bacillus. The glomerular lesions were not present.

of at least part of the lesions. In a number of cases I found that the upper part of the auricular lesion was already organizing or was organized, while other parts of the lesions were active and filled with bacteria. I also found a tendency to lime deposition in chordæ tendineæ which were covered by vegetations. And even in extensive vegetations on the aortic valve, which on the whole appeared to be quite active, marked calcareous deposits could be found. It was of the greatest interest to observe the transitions between the lesions in active cases and the lesions we were beginning to find in the cases which I believed to represent healed cases of the disease in question.

The cases in the last mentioned group, including the first case above described, now number 11.

Case 2. The clinical diagnosis was chronic endocarditis, chronic nephritis, uremia. In the heart there was an organized lesion of the wall of the left auricle. The chordæ tendineæ were thickened, deformed, some were shortened, some torn. One blood culture was made during life, which gave a negative result. The lesions were bacteria-free. Glomerular lesions were found.

Case 3. A case considered to be possibly a case of subacute bacterial endocarditis in which the bacterial infection was over. Death was due to exhaustion from anemia and to an embolic aneurysm of the femoral artery. Three blood cultures were made with negative result. At autopsy there were characteristic lesions of the left auricle and the chordæ, partly organized. There were few poorly staining cocci in the non-organized part of the lesions which could not be cultivated. Characteristic glomerular lesions were found.

Case 4. The clinical diagnosis was chronic endocarditis and chronic nephritis. Characteristic lesions in healing state were found post mortem bacteria-free. There was no blood culture during life. Glomerular lesions were found.

Case 5. This case is of particular interest. I had the opportunity of personally observing this patient last summer, in the service of Dr. J. Rudisch. He was a type of case usually termed "chronic endocarditis with fever." Certain clinical phenomena led me to believe that the case was one of bacterial endocarditis in

which the causative bacteria were no longer present and that the continuance of the clinical phenomena was due to the fact that there was a large calcareous mass on the aortic valve from which pieces were continually breaking off, the calcareous mass representing the attempt at healing of a large mass of vegetations. At autopsy the conditions were as suspected during life. There was a large calcareous mass on the valve, and there was some ulceration. As the lesions on the aortic valve are not characteristic in subacute bacterial endocarditis, as those of the mitral usually are, I could not put this case in the group until Dr. Baehr found typical healed glomerular lesions. Two blood cultures were made in this case; both remained sterile. The masses on the valve were bacteria-free.

Cases 6 and 7. When I found thus that a case with the clinical picture of "chronic endocarditis with fever" could really be a case of bacteria-free subacute bacterial endocarditis, I had the kidneys from 2 other such cases examined. One case had calcareous masses on the aortic valve, an aneurysm of the mitral valve, embolic aneurysm of the iliac artery, and a branch of a renal artery. A few of the chordæ tendineæ attached to the anterior mitral flap showed organized vegetations. Three blood cultures were negative in this case. The lesions post mortem were free from bacteria, and typical healed glomerular lesions were found by Dr. Baehr. The other case presented at the postmortem examination calcareous masses on all three flaps of the aortic valve, with some ulceration of the valve. There was also an aneurysm at the position of the membranous septum. Death was due to cerebral embolism. Three blood cultures in this case revealed no bacteria. Healed glomerular lesions were easily found. It is of great interest to compare the heart in this case with another in my collection in which there are vegetations on all three flaps of the aortic valve. Although there are cocci present, and they were still to be found in the blood at the time of death, distinct calcareous impregnations are present. And it is easy to see that this heart might easily look like the one from the bacteria-free case, if the process of calcification were further advanced.

Case 8. This case was suspected of being in the bacteria-free stage of subacute bacterial endocarditis. One blood culture was

made, with negative result. There are slight organized lesions of the aortic valve. There is a granular lesion of the left auricle, and the chordæ tendineæ show typical changes, but in an organizing or organized condition (histological studies not complete). There were no bacteria in the lesions; glomerula lesions were present.

Case 9. This case was also strongly suspected clinically of being one of subacute bacterial endocarditis, that had become bacteria-free. The cause of death appeared to be a cerebral embolism. The autopsy showed a slight healed lesion of the posterior flap of the mitral valve. The chordæ tendineæ attached to this flap showed apparently organized vegetations (histological examination not completed). The changes in the anterior flap were like those seen in active bacterial cases of the disease; the chordæ tendineæ were matted together at their attachment to the valve, and some of them were torn across. All these lesions appeared to be organized. There was one finger-like vegetation attached to the cusp, which hung down into the ventricle as far as the insertion of the chordæ into the papillary muscle. This vegetation did not seem to be as old as the others. The aortic flaps showed very small vegetations, and one cusp was slightly ulcerated.

Three blood cultures were made, all with negative results. The lesions were found bacteria-free—the glomerular lesions were found.

This case we have considered to be one of subacute bacterial endocarditis in the bacteria-free healed (or almost so) stage. The lesions of the chordæ and of the auricle were typical. The absence of glomerular lesions may be explained in one of two ways. The case may have been one due to the endocarditis coccus, notwithstanding the absence of glomerular lesions, for, as Baehr has pointed out, not every one of such cases shows the glomerular lesions. Or the original infecting agent may have been the influenza bacillus. When more of the lesions are cut up, we shall hunt still farther for the cocci.*

Case 10. This case was also suspected clinically of being one of the remarkable instances of healing endocarditis when the patient was in the hospital in December, 1911. A blood culture taken at

* Since writing the above, glomerular lesions have been found in this case.

that time showed no growth. He returned in March, 1912, with an embolism (embolic aneurysm?) of the right brachial artery. Two blood cultures were negative. At the autopsy the usual lesions were found that are characteristic of subacute bacterial endocarditis when the mitral valve is attacked. The lesions seemed to be nearly, if not entirely, organized (examination not finished). There was one unusual lesion, an old ulceration of the posterior flap of the mitral valve. The vegetations were found bacteria-free. The heart blood contained saprophytic bacteria only. Glomerular lesions were easily found.

Case 11. This case was observed much longer than any other case in this group. The patient was constantly seen for nearly ten months, and was several times under observation in the hospital. In all, nine blood cultures were made, some being incubated anaërobically (this was also done in several of the other 11 cases now under discussion). Not a single colony of an organism was ever found. The man died of anemia, exhaustion, and decompensation. At the autopsy there was found extensive deposits of calcareous, fibrous, and thrombotic material on the flaps of the aortic valve. There were perforations of the valves with healed margins; these were clearly due to ulceration. There were also present aneurysms of the sinuses of Valsalva.

Spreads of the vegetations proved bacteria-free. Cultures of the heart blood showed the ordinary streptococcus, evidently a terminal or agonal invader. The kidneys showed the typical glomerular lesions, all healed.

I wish to digress for a moment here to mention a further finding which to me seems quite important, and to which hitherto no attention has been paid. This patient had the sternal tenderness which I described in an earlier paper as being such a frequent, valuable symptom in subacute bacterial endocarditis, and he had it to an unusually marked degree. I had suspected that it was due to active regeneration in the bone marrow, this being an effort at compensation for the marked progressive anemia so common in the disease. There was another possibility to be entertained, although it was less likely—namely, embolic disease of the bone marrow.

When we performed the autopsy in this last case, we were able to

obtain bone marrow from the tibia, femur, and sternum. In the femur and sternum and in the middle of the tibia the marrow was dark brownish red in color, very firm. It is now being studied histologically.

We have then before us 11 cases in which we have every reason to believe that we are dealing with cases in which patients who had a subacute bacterial endocarditis overcame the infecting agent without their having been seen at a time when the infection was still active. In one, poorly staining cocci were still seen in small numbers in part of the lesions. In 7 of the cases the mitral valve was involved in a way seen practically only in subacute bacterial endocarditis. As 95 per cent. of our active cases were found to be due to the endocarditis coccus, it is fair to assume that nearly all of the 7 cases were due to the coccus. Besides which we have further evidence in the presence of the characteristic glomerular lesions in all of them.

One case had a calcareous mass on the aortic valve, and involvement of chordæ tendineæ in the characteristic fashion. The latter lesion is in itself suggestive, and besides typical glomerular lesions were found.

We have left 3 other cases in which only the aortic valve was involved, and in which large calcareous lesions were found. In all of these we have the proof afforded by the presence of the glomerular lesions that they were the result of infections by the endocarditis coccus. And I have shown you transition stages to these lesions in cases which still had the cocci in the blood during life and in the lesions post mortem.

It is of interest to note in the cases with aortic involvement (calcareous masses on the valve) that aneurysms are frequent, and that they are of a different type from the bacterial embolic type. One finds aneurysms of the sinuses of Valsalva, the heart wall just below the valve, aortic flap of mitral valve, and peripheral arteries. All except the last seem to be due to impact by the calcific material on the valve. They are smooth walled; the peripheral aneurysms seem to be due to the traumatism to the wall inflicted by a piece of lime whipped off from the valve. Some years ago I pointed out that such non-infective embolic aneurysms actually existed.[8]

The question will now be asked, How often does one see a case of subacute bacterial endocarditis in which blood cultures have been positive become bacteria-free, and go on with symptoms due to the changes left in the heart or recover completely? As regards this point, our own experience has been that all the cases in which we found bacteria in the blood and which we could follow went on to a fatal termination with bacteria still present in the blood. In but few cases did the blood cultures become negative, and these patients also soon succumbed. In one case of infection by the influenza bacillus, five blood cultures were positive, and four later ones were negative. This patient died a couple of months after leaving the hospital, or about four months after the cultures became negative. He left the hospital quite anemic, and died of exhaustion and decompensation. An autopsy was not permitted. Our experience coincides with that of those who have seen large numbers of these cases. The instances of recovery in cases with positive blood cultures will be cited briefly later in the discussion of the literature.

It is curious, in view of the facts just stated, that there should exist so many cases* which must have had a bacterial infection, have recovered from the infection, and have certain clinical pictures from the changes brought about during the infective period. We must assume that in these cases the period of bacterial infection was very short, as compared to the cases which we see with bacteria in the blood, or very short and very mild. When one sees cases of the disease with bacteria demonstrable in the blood go about for many weeks with hardly any symptoms, it is not difficult to believe that some patients with a mild or short infection may not feel sick enough to ask for medical attention, or present such mild clinical pictures that they are not put to bed. That the infection in such cases is a shorter one is also suggested by the study of the glomerular lesions. They were found to be much more abundant in cases in which cocci had been found in the blood than in those in which they were never demonstrated.

It is not my purpose in this communication to discuss at length

* I have seen a number of cases besides those mentioned in the text which I believed to be examples of bacteria-free cases. Some have disappeared from observation. A few I am still following. I believe we will be surprised at the number of such cases that exist and which we have hitherto not properly interpreted.

the clinical pictures presented by the cases with healing or healed lesions. A sufficient number of cases has not yet been collected to give us a clear idea of the complete course of such cases. It will be important to determine how long people with this condition can live, and whether any of them, after the bacterial infection is over, can live for many years with no more trouble than they had from their original valvular lesion before the infection was superimposed. My own data are too few to give any definite facts. But two observations are of some value. One case (Case 11) was observed in a bacteria-free condition almost ten months. I have another case under clinical observation, who has but few symptoms, who is in no worse condition to-day (perhaps even better) than he was ten months ago.

As far as the data, which I have thus far at my command, go, they indicate that the cases with healing or healed lesions present the following clinical pictures:

1. They go on to have a nephritis and die of uremia.

2. They present the picture corresponding to what we have been wont to call "chronic endocarditis with fever" (that is, they have a valvular lesion, more or less fever from time to time, usually low, occasional petechiæ,* occasional joint symptoms, and embolisms). Some of these cases closely resemble cases in which bacteria are demonstrable in the blood. The differences will be discussed when I have more material. Some of these patients are pale and some more or less pigmented (see below).

3. Some of these cases present a clinical complex that appears to have been entirely overlooked. The striking feature is a peculiar diffuse brown (sometimes quite dark) color of the face. The rest of the body may show some pigmentation. There is evidence of a valvular lesion, there is more or less anemia, usually a palpable spleen, and usually also tenderness of the lower sternum.† The patients feel weak and do not sleep well. Petechiæ occasionally occur. There is temperature from time to time, usually low. Erythrocytes are found in the urine in at least some of the cases. The

* My investigations go to show that purpura occurs particularly in the cases with calcific masses in the valves.

† This symptom will be more fully discussed in a separate publication, as will also the changes in the urine.

subsequent history of such cases is not yet known. One case died of cerebral embolism.

I wish particularly to emphasize the curious change in the color of the face. It will, I am sure, be of great importance in the recognition of some of the cases with healing or healed lesions. Since I have observed it in such cases, I have looked for it in cases with bacteria in the blood. And now, to my surprise, I find that while the faces of most of the cases are sallow, or of a rather white color, some develop a certain amount of brown or café-au-lait color.

4. They may go on with more or less anemia, and suffer from that and from decompensation.

I would like now to note a few of the important symptoms that occur in the bacterial cases, and state what my experience is as regards them in the cases in which the infection has been overcome:

1. Fever. This is found in all of the non-bacterial cases that we have observed, but it is a less marked feature, and the temperatures are low for much longer periods. In a paper published in 1906 I expressed the opinion that the fever in such cases may at times be due to the discharge into the blood current of bits of old vegetations or thrombotic masses, even if they contained no bacteria. Bock,[21] in a paper just published, has shown that fever can be experimentally produced by the intravenous injection of bacteria-free, chemically indifferent particles.

2. Splenic Enlargement. This symptom seems to persist in the non-bacterial stage. I have reason to suspect that occasionally when the spleen is very large, the clinical diagnosis may appear to be a splenic disorder plus chronic endocarditis.

3. Pains. These may be just as severe in the bacteria-free cases. The same holds true of joint pains.

4. Painful Erythematous Nodules. These were not observed in the bacteria-free cases, except in one case, in which they were a prominent feature during the early period of the observation.

5. Sternal Tenderness. This symptom, on which I lay much stress, is equally frequently met with in both groups of cases. It even seems to be a more marked symptom in the bacteria-free cases. As I have stated in an earlier publication,[1] sternal tenderness may be found even when the hemoglobin is not markedly reduced.

6. Petechiæ. These occur in the bacteria-free cases, but are not as abundant and do not occur so frequently. Purpura seems to be a feature rather of some of the bacteria-free cases.

7. Hematuria. This subject needs further investigation. Erythrocytes were found in the urines of those cases of the bacteria-free group in which they were carefully looked for. Gross hematuria, that is to say, smoky urine, I remember to have seen only once in the cases in the bacteria-free group, and it occurred in that case only during the early part of the period of observation.

Other symptoms, such as sweats, the blood changes, the gastrointestinal phenomena, etc., will be discussed when more data are available. The facts that I have given show the close resemblance between many of the features in the two groups of cases. It is important that we can recognize at least some of the bacteria-free cases quite definitely. It will be of great value to recognize such cases, and make studies of the serum. Complement fixation studies made in such cases may lead up to our being able to determine the exact status of the cases classed as chronic rheumatic endocarditis. We may be able to ascertain whether there exist cases that have had the bacterial infection and have completely recovered, being left with symptoms from the original valvular lesion due usually to rheumatism.

It will finally be of interest to take a glance at the literature on the subject of healing of the lesions of subacute bacterial endocarditis. I shall take up at the present time almost only the experience of authors who had the advantage of having blood cultures made in their cases. The question of the possibility of the healing of acute endocarditis I shall not discuss at this time. Herrick[9] has discussed that subject fully.

Litten,[10] Leyden,*[11] Osler,[3] and Rosenow[12] do not record any with bacteria-free cases.

Harbitz[4] in the report of his admirable investigations on endocarditis discusses lesions that he found in 10 cases that he believes were related to "chronic infectious endocarditis," which lesions he

* Leyden believed that it was possible for "ulcerative" endocarditis to heal. He evidently had instances of subacute bacterial endocarditis among the cases he studied, but none with healed lesions.

believed were in a healing stage.* He says that he did not succeed in obtaining bacteria in these lesions, but the anatomical picture, "the extension to the walls of the auricle and ventricle, the excrescences on corresponding parts of two adjacent flaps, the tearing of chordæ tendineæ, etc.," was quite characteristic. These cases ran a long course, at times associated with subacute nephritis. In one case of this group, in which the cultures at the autopsy were sterile, Peter Holst obtained, two weeks before death, a "white staphylococcus" in the blood. In a few cases, indistinct groups of organisms in sections and smears and the cultures were negative. These observations of Harbitz are the most definite hitherto recorded.

Bartel[13] made a study of twenty-two hearts from cases of endocarditis to determine whether "ulcerative" endocarditis is capable of healing and how often it occurs. His cases, 4 and 7, resemble much some of the cases I have described. He discusses the possibility of relapses of infection due to bacteria lying dormant in healing or healed lesions, a subject that is worthy of further study, as I have pointed out on a former occasion.[20]

Lenhartz[14] states that none of his cases recovered. One case that left the hospital after the fever had disappeared, and the blood was free from bacteria, died ten months later of cardiac insufficiency. Horder[15] saw only one recovery in 150 cases of endocarditis due to all kinds of bacteria. The patient was a boy, aged fifteen years, who had fever for seven weeks. He eventually lost all evidences of cardiac disease. This observation loses in value because no blood culture was made.

Latham and Hunt[16] describe the case of a man who was under observation from August 24, 1909, to November, 1910. They obtained a coccus from the blood which may very well correspond to the endocarditis coccus, seven times between October and July. There was irregular fever and repeated embolisms. From April on there was gradual improvement. When the patient was seen in November, 1910, the temperature had been normal or subnormal for several months, the pulse rate was 60, and the heart was regular

* I am indebted to Dr. Baehr for drawing my attention to these ten cases described by Harbitz.

The mitral systolic and aortic diastolic murmur persisted. The last three blood cultures were negative.*

The authors ascribe the recovery to the use of an autogenous vaccine administered by mouth. As one so often sees spontaneous disappearance of the bacteria, this case may very well have become bacteria-free without the use of the vaccine. Vaccines have been used by many competent observers in these cases without any beneficial effect.

Emerson and Harrison[17] describe a case supposed to be one of the group under discussion, but it does not seem to me to be a case of subacute bacterial endocarditis.

Schottmüller,[18] in 1910, described 5 cases of subacute bacterial endocarditis ("endocarditis lenta"), and stated that one was still under observation, and was doing well. The other four died. He has not reported since that time on the case that he believed was recovering.†

Jochmann[19] has recently reported 7 cases of the disease. Two of these cases recovered. Three of the cases were treated with an autogenous vaccine and with a serum produced by immunizing animals with cultures of the "Streptococcus viridanes." Two of the patients so treated died. So that one case recovered on the use of specific treatment, and one without it. It is to be hoped that the subsequent course of these two cases will be reported.

Some time ago I came across a reference to a case mentioned by Reiche, of Hamburg, at a meeting. He had a case of subacute bacterial endocarditis in which the blood cultures became negative after they had shown cocci a number of times. The patient died of an embolic aneurysm of an intrahepatic branch of the hepatic artery, which had ruptured into the liver substance, and caused a fatal hemorrhage into the peritoneal cavity. The endocardial lesions, Reiche stated, were found healed. It is unfortunate that no further data are given as to bacteriological studies of the diseased valve and no accurate description of its appearance.

* The authors make a note that the polynuclear percentage dropped from 74 to 54 in the course of the case. I have a number of times seen lymphocytic increase in subacute bacterial endocarditis, in cases with and without bacteria.

† July 31, 1912.—Since this paper was written I have heard from Professor Schottmüller that this case has succumbed.

It will be noted that the observations on the healing of subacute bacterial endocarditis are rather few in number. From the pathological standpoint, those of Harbitz are the most illuminating. From the standpoint of healing in a clinical sense, the observations of Latham and Hunt and Reiche and Jochmann are important. It is essential that writers who in future report such cases, give subsequent reports on the condition of the patients, with reference to the clinical points I have discussed in the body of the paper. It seems remarkable that the cases that have spontaneously become bacteria-free have hitherto escaped detection.

I believe I have brought forward sufficient evidence to prove that subacute bacterial endocarditis is a disease in which healing can occur from the bacteriological, pathological, and clinical standpoints. The evidence of complete healing, from a clinical standpoint, is meagre.

It is a pleasant duty for me to express my gratitude to Drs. Rudisch, Meyer, Brill and Manges, the visiting physicians to Mount Sinai Hospital, for their great kindness during many years in permitting me to make studies on their cases. The clinical data are mainly derived from the cases in the service of Dr. Rudisch, and from cases which a number of physicians permitted me to observe in their practice. I must add that it would not have been possible to complete the bacteriological and pathological studies, so far as they have been carried, without the enthusiastic assistance of the various members of the laboratory staff for the past ten years.

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DISCUSSION

Dr. Harlow Brooks: I think personally that Dr. Libman overestimates the specificity of the symptoms of sternal tenderness in this condition, if I understand him correctly in this particular. This sign is very frequently demonstrable, for example, in cases of syphilitic myocarditis, and I believe also in other types of endocarditis as well as in some instances of pericarditis.

Dr. James B. Herrick: Dr. Libman has referred to a paper which I read here a few years ago, in which I spoke of recovery of one case of endocarditis, and in which I collected from the literature other instances. Since that time it has been my fortune to see quite a number of cases of this subacute type of ulcerative endocarditis which Dr. Libman describes. I have never seen another case recover. I have seen death postponed for nine or ten months, but the disease has been uniformly fatal.

Dr. George Dock: There is a new feature in regard to the practical diagnosis of these cases, and that is the increase of tropical diseases. Formerly all these cases were called malarial by somebody in the course of their existence, but now that there is so much access to the tropics and so much more is known about the tropical affections, they are known by other names. This is brought to my mind by a recent case I saw. In the first place the man was treated for malaria chiefly because he had been living in Honduras and had a remittent fever, and an enormous amount of time was spent in looking for the malarial organism in the blood. Then he was treated for Leishmaniosis. Then he was treated for Malta fever, because he had a temperature which corresponded fairly with that of Malta fever, and all sorts of rare tropical parasites were looked for in his blood. In that case a source of difficulty was that there was not an enlarged heart. If you make a diagnosis of malignant endocarditis in such a case and go on farther and name the valve, usually the first answer of the doctor is, "I though of that, but the heart is not enlarged." The

reason the heart is not enlarged, I take it, is the patients are taken seriously sick so early in the disease that they soon stop work. A patient with suspected malaria, with some sort of fever, with malignant endocarditis, usually feels himself a sick man. His case is regarded as an interesting one in the hospital, trained nurses take care of him, and he does not exert himself. For various reasons in mitral stenosis the heart is not enlarged, and an interesting point in mitral stenosis, the presystolic murmur, is not present. A direct systolic murmur is not conducted well up into the axilla, so that the murmur is readily taken by the doctor for a functional murmur due to the patient's anemia. The whole question in practical diagnosis is still one of considerable confusion and such a demonstration as this and such an account as Dr. Libman has given of the great amount of material observed by him ought to do a good deal in clearing up these cases.

Dr. Alexander McPhedran. I have seen a well-marked case of this kind recover. Such was the case in a young woman whom I saw many times with one of my junior colleagues many years ago. She had all the characteristic symptoms such as occur in chronic endocarditis. The spleen was large and the patient was very seriously ill. The outlook was not encouraging. This was some years ago and no cultures of the blood were made. She made a complete recovery, was married, and has two healthy children.

Dr. Libman: In regard to Dr. Herrick's question, I would say that all of the cases in which the blood cultures were positive and which we were able to follow up succumbed. Those that spontaneously recover from the infection must have an infection of short duration. This is more fully discussed in the full paper.

As Dr. Dock has stated, it is remarkable how little the cardiac murmur change in the course of this disease, and how little the walls may increase in thickness. I have generally ascribed this, at least in part, to the fact that the recent lesion involves the walls of the auricle and the chordæ tendineæ rather than the valve itself.

In answer to Dr. Brooks' remarks, I would say that I did not intend to have it appear that I believe that sternal tenderness is pathognomonic of this disease. Sternal tenderness occurs in pernicious anemia, in all systemic diseases of the bone marrow, and in some other conditions. What I wanted to bring out was that when one sees a patient with a valvular lesion, and the sternum is tender, and particularly if there is pigmentation of the face, one should examine the case farther and observe it and see whether it is not a case of subacute bacterial endocarditis in the bacteria-free stage.

Not every case presents this symptom of sternal tenderness. This in itself would not be surprising, because its presence depends a great deal

upon whether the patient is sensitive to pain or not. There are patients who are hypersensitive to pain and others almost insensible to pain (this I shall discuss at another time), and in these latter patients clinical pictures, of which pain is usually a component part, are often incomplete. We have made a limited number of studies as to the value of transfusion in these cases, and thus far all I can say is that the transfusion strengthens the patient and gives him a longer time to fight, but I have hitherto seen no direct curative result.

GLOMERULAR LESIONS OF SUBACUTE BACTERIAL ENDOCARDITIS

By GEORGE BAEHR, M.D.[1]
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In the kidneys of nearly all individuals dying during the course of subacute bacterial endocarditis, there exists a pathological lesion which affects one or more loops of a variable proportion of the glomeruli.[2]

The first to draw attention to this lesion and to connect it with infections of the endocardium by the endocarditis coccus (Streptococcus veridans) was Loehlein. In March, 1910, he reported 8 cases of this condition, in all of which loops of some of the glomeruli showed the lesions. Three of these showed organisms in blood cultures taken during life, and in one of these, organisms were cultivated from vegetation post mortem. In one case the lumen of an artery entering an infarcted area was occluded by an embolus which contained numbers of cocci.

Before proceeding to a consideration of the glomerular lesions, it is necessary to understand a few of the cultural characteristics of the endocarditis coccus in order to be able to appreciate the mechanism by which the kidney lesions are produced. On the surface of agar its growth is exceedingly dry and sometimes difficult to remove. When an attempt is made to emulsify this growth in normal salt solution, the bacteria show a very marked tendency to hang together in small firm clumps which usually cannot be broken up even by very vigorous shaking.

[1] Presented by Dr. E. Libman. This work was carried on under the tenure of the Eugene Meyer, Jr., Fellowship in Pathology of Mount Sinai Hospital.

[2] For a full discussion of this subject, see the paper which was published in the Jour. of Exper. Med., vol. xv, p. 330.

Smears made from pieces of vegetations in these cases when squeezed between slides and stained by Gram's method usually show the presence of the typical cocci in numbers such as are seen only in smears made from pure cultures. It is quite conceivable, therefore, that large numbers of these clumps are constantly being washed off the vegetations by the blood current, and being just small enough to pass the vasa afferentia in the kidney, become lodged in the capillary loops of the glomeruli.

In the kidneys of individuals dying during the active bacterial stage of the disease there are seen, as a rule, all stages of the glomerular lesions. The number of involved loops of a glomerular tuft varies in the different diseased Malpighian bodies. Furthermore, there is a great variation in the relative number of glomeruli involved in different parts of the kidneys. The uninvolved glomeruli and the uninvolved loops of involved glomeruli show no changes.

The very earliest stage of the process appears to consist of a swelling of the glomerular epithelium in the involved loops. This may be situated at any portion of the glomerular tuft. If the lesion is large, a segment of the glomerulus, or even the entire Malpighian body, may be involved by the processs. At first the outlines of the swollen epithelial cells in the diseased segment can be made out. Subsequently they are lost and the entire structure is fused into a homogeneous, finely granular material. In this mass some of the nuclei are fading or undergoing karyorrhexis, although a few may still remain fairly well preserved.

If the deep staining, finely granular mass is situated at the periphery of the glomerulus the epithelium of the visceral layer of Bowman's capsule over the involved part is usually found to be swollen, proliferating, and desquamating into the capsular space. When the mass with its overlying epithelium comes into contact with the parietal layer of Bowman's capsule the latter then probably also takes a share in the desquamation, and perhaps in the proliferation.

Eventually this epithelium undergoes necrosis, as did the previously swollen epithelium of the involved loops of the glomerulus. It also becomes part of the homogeneous, finely granular mass which now fuses with the parietal layer of Bowman's capsule. At

this stage the mass may become flattened out over the area of fusion with Bowman's capsule in a crescentic fashion.

The homogeneous cellular material is seen to be traversed by a very delicate network. Eventually the entire mass becomes thoroughly organized. At the same time there occurs active growth of the epithelial cells of the adjacent intact portions of the parietal layer of Bowman's capsule. They advance over the inner aspect of the necrotic mass which by this time has usually separated somewhat from the rest of the glomerulus. Eventually the entire lateral surfaces of the mass are covered by this invading epithelium.

The healed stage of the lesion presents the following picture: A hyaline mass having roughly the shape of a truncated pyramid; its base fused with the adjacent interstitial tissue; its mesial aspect adherent to the remainder of the glomerulus; its sides clothed by a reflection from the adjacent epithelium of Bowman's capsule.

When the entire glomerulus is involved, the peripheral portion may be seen to be replaced by concentric fibrils of connective tissue, whereas the central portion still consists of a homogeneous material. In the same section, however, examples of even later stages are frequently seen, the glomerulus being entirely replaced by a mass of hyaline fibrous tissue.

Practically every stage of the process described above is to be seen in nearly every microscopic section of the kidney cortex from most of the cases, and this association of the various stages is an important part of the pathologic picture.

The typical lesions were found in 23 of the 25 cases due to the endocarditis coccus. In 2 cases, 1 of which was due to the influenza bacillus and 1 due to the gonococcus, the lesions were not found. The percentage of glomeruli involved varied from 2 to 75 per cent. in various cases.

In sections of 5 cases in which portions of the kidneys were fixed in alcohol, Gram-Weigert stains demonstrated bacterial emboli in the capillaries of the glomeruli. In 2 cases they were easily found; in the other 3 they were discovered only after prolonged search.

The changes that occur in the tubules and interstitium, and in the end may lead to a picture identical with that of the secondary

contracted kidney, are discussed in the paper already referred to. In the same paper will be found a description of the atypical lesions which were found in two cases, and which closely resembled the lesions found in subacute glomerular nephritis.

In 54 cases of acute endocarditis due to the ordinary pathogenic bacteria none of the glomerular lesions were found in any case. In the cases which Dr. Libman has described as being instances of a healed or bacteria-free stage of subacute bacterial endocarditis the characteristic lesions were found every time, only the healed stage of the lesion being present. In these cases the lesions were less abundant than in cases in which the endocarditis coccus had been found during life or after death.

RHEUMATIC FEVER AND THE ARTERIES

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Cardiac lesions are no longer considered as complications of acute rheumatic fever, but are just as much a part of the disease as the affection of the joints. The frequency of the association of pericarditis, endocarditis, and myocarditis or any one of them with other lesions making up the picture of acute rheumatism is very great, and I think many will agree with Aschoff that every attack of rheumatic fever leaves its mark on the heart. It has been particularly emphasized that the myocardium is most often affected, and this for the reason, as we shall subsequently indicate, that the reactions to rheumatism occur in the neighborhood of the fine nutrient vessels of the myocardium. Inflammatory exudates occur about these fine arteries, and are replaced in the chronic stages of the disease, by fibrosis.

In general our conception of acute rheumatic fever is being modified with the progress of the pathological studies made upon it. That it belongs to the acute infections no one will deny, and many are willing to place a considerable stress upon the organism of Poynton and Paine as the causative agent. Whether it is the initial factor, or whether some other condition predisposes to the invasion of the diplococcus rheumaticus, we cannot here argue; but it is more than probable that the lesions as we find them in diverse parts of the body are the result of the action of these diplococci.

In the late stages of the disease process we not infrequently observe the association of heart, kidney, and arterial lesions making up a picture very different from that of acute rheumatic fever.

Nevertheless we are compelled to admit that all of them are either the result of the primary acute process or else that in the process of a vicious circle one lesion has followed the other. A close study of the various organs can alone determine the direct effect of this systemic disease upon each, and with this in view I have followed, in a few cases, the lesions to be observed in the arteries and more particularly the aorta during the course and different stages of rheumatism. This study presents purely the pathological side of the question. The cases studied were selected from a series of autopsies, only those being taken in which one or more previous attacks of acute rheumatic fever were established in the clinical history and in the presence of interstitial myocarditis.

In classifying the cases here examined I have divided them into three groups: (1) Acute rheumatic fever, first attack; (2) recurrent rheumatic fever, and (3) chronic rheumatism. It was interesting to find that the changes in certain arteries were analogous to the lesions found in the heart in the different stages of the disease; in fact, the resemblance of the inflammatory reaction in the aorta to that of the myocardium was very great. It may, however, at the very beginning, be pointed out that the causative agent of acute rheumatic fever has a predilection for the perivascular tissues of the smaller vessels, the arterioles, and does not appear to disturb the larger arteries directly, save by damage in the vicinity of the vasa vasorum. Up to the present I have not made a systematic study of the arterioles of all the viscera of the body. My observations have, however, indicated that the arterioles of the internal organs, except the circulatory system, are not attacked with any constancy.

The aorta shows a fairly typical lesion. This lesion is particularly to be observed in the ascending limb and in the arch, less frequently in the descending thoracic and seldom in the abdominal aorta. The distribution of the process in the aorta is similar to that of syphilis, and, as a matter of fact, to that of many bacterial infections. The main coronary arteries of the heart are inconstantly involved, while, on the other hand, the finer ramifications of this vessel are invariably affected, being a part of the myocardial disease which forms an important factor in the pathological picture of rheumatic fever. Moreover, the arterioles passing to the serous

cavities, particularly the pericardium and the joints, partake of a reaction similar to that of the nutrient arteries of the aorta and heart. In how far the vessels of the meninges and the abdominal viscera respond to the irritant present in rheumatism I am not prepared to say.

Acute Rheumatic Fever (First Attack). Of such cases I have had only three to autopsy, aged nine, sixteen, and nineteen years respectively. All of them had associated cardiac disease, two with pericarditis, all with acute interstitial myocarditis, two with fresh mitral deposits, and one with recent mitral and aortic vegetations. The youngest case had suffered choreiform attacks during his illness.

The arterial findings being similar in these cases a single description will suffice. Macroscopically the arteries were but little changed, the oldest individual alone showing superficial fatty streaks in the intima. The elasticity of the aorta was not altered and none showed the inflammatory foci to the naked eye. Microscopically, however, there was a very striking picture present in each case. Sections of the ascending and transverse portions of the aorta showed that the intima was not thickened and the lamellæ of the media appeared regularly disposed. In the media, however, the arterioles appeared more prominent than usual, and these nutrient vessels encroached beyond the outer third into the muscularis. These arterioles had an edematous perivascular infiltration in which aggregations of lymphocytes and plasma cells were constantly found. Moreover, the elastic fibers of the media in this vicinity were interrupted, often appearing as if mechanically broken. Muscle elements of the media in the neighborhood of the vasa vasorum had also, in part, disappeared, an indication of some local toxic agent surrounding the nutrient vessels.

In the adventitia the infiltration by inflammatory cells was very extensive. Lymphocytes and plasma cells were diffusely scattered through the tissue, while more densely aggregated cells were seen about some of the vessels. Polymorphonuclear leukocytes were also seen, but in relatively small numbers. Occasionally areas indicating endothelial proliferation were observed in the vicinity of the capillaries. The connective tissue was loose and rather edematous, while the capillaries were much congested. In some of the reactions

fibroblasts were apparent, but no new connective-tissue fibers were observed.

The main coronary arteries of the heart were but little affected, save at the periphery of the adventitia. The smaller arterioles, however, showed a dense infiltration about them, with a considerable change in the appearance of the heart tissue in the immediate vicinity. In places the infiltrating cells were mainly lymphocytes, while in others again leukocytes and endothelial cells appeared to make up the main type of invading cell. The heart muscle adjoining these involved vessels showed evidence of degeneration and not infrequently complete death. In the place of these heart muscle cells there remained a homogeneous and almost structureless material with occasional evidence of replacement by fibroblasts. The perivascular infiltration was very widespread and quite uniform throughout the heart muscle.

It is indicated in the above that the main reaction occurring about the arteries during the acute stage of rheumatic fever is in the outer coats. The adventitia and the media are probably simultaneously involved, at times by way of the nutrient vasa vasorum, or in the case of the smaller vessels, the arterioles, directly from the perivascular lymph stream. The reaction is of the acute non-suppurative variety, in which the lymphoid type of cell and the endothelial cells play the important part. Similar to the reaction in the heart, the tissues of the arteries suffer directly from the harmful agent of acute rheumatism, in which both muscle cells and elastic fibers in the immediate neighborhood are destroyed.

Recurrent Rheumatic Fever. Four cases of recurrent rheumatic fever were studied. Their ages were twenty-eight, thirty, thirty-six, and forty-four years respectively. In each case there was a history of one or more previous attacks, and the heart showed the presence of subacute and chronic interstitial myocarditis to a varying degree. Moreover, some form of recurrent endocarditis was present in each heart.

Sections of the aorta showed the intima to be fairly intact and with no definite areas of thickening. The arrangement of the media appeared quite normal and regular in its inner half. However, it was observed that the vasa vasorum were quite frequent in the

middle third of the media, and that these small bloodvessels were surrounded by an excessive amount of fibrous tissue, along with a cellular infiltration consisting of lymphocytes, plasma cells, and a few endothelial cells. This perivascular infiltration was quite constant, and at times the aggregation of wandering cells was quite marked. In some areas it was definitely indicated that some of the muscle cells and elastic fibers had been destroyed and their place taken by a meshwork of new connective tissue. Polymorphonuclear leukocytes were for the most part wanting.

The adventitia also showed a lymphocytic infiltration around the vasa, as well as an increase in the connective tissue close to the media. Some of the nutrient vessels showed a thickening of their walls with a narrowing of their lumina.

It is evident that in these cases of recurrent rheumatic fever certain changes have been produced about the aorta, which subsequently lead to an increase of fibrous tissue in the outer portion of the media and in the adventitia. Moreover, it would appear that with each recurrent attack of the disease a new non-suppurative inflammatory reaction occurs in the sites of the former lesion. Therefore in the recurrent types of the disease various stages of the inflammatory process may be observed in the same specimen. The former attacks are indicated in the presence of adult connective tissue, while the recent progressive condition is seen in the non-suppurative inflammatory infiltration.

Chronic Rheumatism. All of the eight cases considered in this class were such as had suffered, for a considerable time, recurrent or progressive heart disease associated with acute rheumatic fever. The majority had died of broken cardiac compensation. The most constant cardiac finding was a chronic interstitial myocarditis, while an old endocarditis involving one or other of the valves was not uncommon. In this series of cases the lesions of the aorta and of the smaller coronary arteries was quite constant, but varied in the extent of the reaction. Macroscopically the intima was more or less nodular. At times the thickening of the intima was quite extensive, while, however, it showed little evidence of degeneration or atheromatous change. There was usually a great loss in the elasticity of the entire vessel wall, and the artery felt thicker and heavier.

Sections of the aorta showed that the thickened intima consisted mainly of a hyaline looking fibrous tissue, in which numerous fine elastic fibers were seen. The media appeared compact and dense, and the muscle cells did not appear as frequent as usual. The vasa vasorum were seen commonly in the middle third of the media, and some were found in the inner third. The majority of these vessels had their direction parallel to the elastic fibers and a considerable number were surrounded by a fibrous tissue, which had replaced the muscle cells and interrupted the concentric layers of elastic fibers. A slight lymphocytic infiltration surrounded many of them, and plasma cells were also present. Polymorphonuclear leukocytes were not present. In the adventitia there was a fairly dense stroma of connective tissue built closely upon the outer border of the media, so that the thickness of the entire wall was increased. The small bloodvessels were not congested, but in their vicinity there were some scattered lymphocytes. The vasa vasorum in the adventitia had thickened walls.

The changes observed in the vicinity of the coronary arteries of the heart are those with which we are all familiar in chronic interstitial myocarditis. In fact, these very interstitial myocardial changes which have attracted our attention are the result of non-suppurative processes occurring in the neighborhood of the finer coronary arteries. Thus the pathological process about the arteries in the late stages of rheumatic fever is one of inflammatory fibrosis. This fibrosis is particularly evident in the first part of the aorta and about the smaller branches of the coronary artery of the heart.

Discussion. There appears to be a fairly definite form of arterial disease which is associated with rheumatic fever in its different stages. The arteries react to the irritant in a true inflammation and this reaction is to be observed in the adventitia and the outer portion of the media. In the acute stages the inflammatory exudate is of the non-suppurative variety in which the lymphoid cell is most prominent. The inflammation occurs particularly in the neighborhood of the smaller arteries, while the medium-sized vessels are little affected. On the other hand, the larger arteries, which are supplied in their outer coats by nutrient vessels, are damaged by the inflammatory process which travels along the vasa vasorum.

During the acute process the fixed tissues in the immediate neighborhood of the small arterioles are damaged or even destroyed, but abscesses are not formed. In the aorta the destruction of tissue is particularly noted in the loss of muscle and elastic elements. Similar degenerations are common in the heart. At times the degenerative processes are quite extensive, leading to the loss of considerable tissue of the part, and probably weakening the media. The intima of the arteries does not appear to be primarily affected. In the early stages a slight superficial fatty change is sometimes noted, while later, in the chronic stages, the intima proliferates, giving rise to a nodular endarteritis.

The repair, following the inflammatory process of the media and adventitia of the arteries, is by fibrous tissue. Thus the aorta in chronic rheumatism is disturbed by a patchy fibrosis, better spoken of as chronic productive mesaortitis. It is evident that the arteries which are involved in a chronic mesarteritis have lost much of their elasticity and may become subject to a diffuse dilatation of their lumen.

In some respects the acute stage of the mesarteritis resembles the early process of syphilis, but with this difference, that the destruction of the tissues in syphilitic mesarteritis has other qualities, in that the lymphoid infiltration about the vasa vasorum is greater, gummy necroses are often seen, and granulomatous tissue surrounds the areas of greatest reaction. The invasion of the capillaries through the media toward and into the intima is more marked in syphilis, while the nodular endarteritis is also far more decided.

In 1903 Chiari suggested the division of productive mesaortitis (as well as mesarteritis) into two groups, type "A" and type "B" respectively. His type "A" is a chronic inflammatory disease of the media secondary to an intimal process. The mesarteritis type "B" is a primary inflammatory process involving the media, which is usually of infectious origin and most commonly due to syphilis.

As I have on a previous occasion pointed out, Chiari's classification is a good one, but it must always be borne in mind that this type "B" (productive mesaortitis) must include other infectious inflammatory conditions of the media than syphilis. As has been indicated above, the lesions occurring in the arteries in rheumatic fever belong to the group of productive mesarteritis type "B."

A NEW METHOD FOR STUDYING THE BRACHIAL PULSE OF MAN

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AND
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Although the pulse form in the peripheral arteries of man has been the subject of numerous studies, the results of these have proved on the whole rather disappointing. This has been due in part to instrumental defects, in part to the difficulties encountered in the interpretation of pulse forms in general. Sphygmographic tracings are so markedly influenced by the manner in which the instrument is applied that they are almost useless for accurate studies. The pulsations obtained from a plethysmograph record the changes in arm volume caused by the intermittent influx of blood. Unfortunately they give no direct information as to the blood flow. Similarly the tachograph of v. Kries records at best variations in the velocity of blood flow without recording the constant velocity upon which these variations are superimposed.

For some time we have been using a method suggested by Brodie and Russell for the study of the blood flow in the arm. The venous outflow from the arm is obstructed by suddenly inflating a circular cuff to a pressure somewhat below that which prevails in the arteries. As a result of this venous obstruction the arm swells, owing to the entrance of arterial blood and for a brief period this swelling represents the normal blood flow to the part. Volume tracings of the arm taken at this time always show the arterial pulsations; and just as the average rate of inflow is recorded by the average rate at which the arm swells, so the inflow during each

portion of the pulse cycle is recorded by the momentary variations in arm volume. Since the chief inflow to the portion of arm studied is through the brachial artery, we obtain by this means an approximate record of the volume flow in the brachial artery during each portion of the pulse cycle.

The accuracy of these records depends in the main upon two factors. In the first place it depends upon the correctness of the assumption that the veins are completely occluded and the arteries opened throughout the brief period during which tracings are taken. This has been discussed in a previous communication, and subsequent work has confirmed us in the belief that with good technique the error from this source does not exceed 20 per cent., and is usually much less. The accuracy of the records depends furthermore upon the employment of a recording device, which will follow rapidly and accurately the changes in arm volume produced by the arterial pulse waves. For this purpose the ordinary volume recorder is not sufficiently rapid, and we have therefore used a Frank capsule where the writing lever of the Marey tambour is replaced by an imponderable beam of light. This instrument may be graduated so as to give quantitative records of volume changes, and we have furthermore constantly compared its records with those of the volume recorder.

A single normal individual was studied under varying conditions which affected the blood flow in the arm and the form of the pulse. A limited number of observations were also made on individuals with abnormal forms of pulse.

The normal individual was first studied during varying room temperatures in order to determine the effect of local variations of blood flow upon the form of the pulse as recorded in this manner. In the individual studied the blood flow in the arm varied from 3 c.c. to 6 c.c. of blood flow per 100 c.c. of arm substance per minute during agreeable room temperatures. During marked chilliness it fell to 1.5 c.c., and during uncomfortable warmth it rose to 13.7 c.c. During agreeable room temperatures the major portion of the blood entered the plethysmograph during each primary systolic pulse wave. Thereafter to the next systolic wave little if any blood entered. At this time

the blood flow in the brachial artery was nearly at a standstill, save for slight oscillations. Frequently some of these latter showed negative phases, which probably indicated momentary reflex movements in the column of blood in the brachial artery. These negative waves, however, were never so definite as after the use of nitroglycerin, which will be discussed later. When the room was cooled and the individual felt chilly, the pulse rate was slightly slowed and the size of the primary pulse waves reduced.

The following table shows the relation between the rate of blood flow in the arm and the height of the pulse wave in the plethysmogram in the same individual on various occasions. The variations in the blood flow were produced by variations in room temperature. Note that without nitroglycerin the height of the pulse waves varied with the rate of blood flow, while with nitroglycerin they remained nearly constant and maximal.

Without nitroglycerin.			With nitroglycerin.		
Rate of blood flow.	Height of wave.	Pulse rate.	Rate of blood flow	Height of wave.	Pulse rate.
1.5	0.36	60	1.5	0.86	72
2 0	0.26	66	1.7	1.09	72
3.1	0.77	70	2.1	1.10	75
6.3	0.96	72	4.6	1.06	75
6.9	0.95	74	5.4	0.95	78
13.7	0.90	87	5.2	1 20	74
			6 0	1.20	72

The chief inflow continued to take place during the primary pulse waves, and little or no inflow occurred during the remainder of the pulse period. In some tracings from this as well as from other individuals there was a slight back flow in the brachial artery throughout the period following the primary pulse wave. When the room temperature was raised sufficiently to cause uncomfortable warmth, the blood flow in the arm was increased to 13.7 c.c. per 100 c.c. of arm substance per minute. At this time the primary pulse wave was not materially increased over that seen at the upper limit of the usual flow, but in place of an almost stationary stream following the primary wave there was now a continued influx of blood throughout this portion of the pulse period.

In order to explain these observations we must consider (1) the

factors which influence the size of the primary pulse wave and (2) those which determine the general rate of blood flow in the arm. The primary pulse wave is produced by the systolic output from the heart, and is modified by the arteries which conduct this wave to the arm. In our opinion its size depends chiefly upon the size of the brachial artery, being larger when the artery is relaxed and smaller when it is contracted. The average blood flow in the arm, on the other hand, depends in part upon the average blood pressure, but chiefly upon the degree of constriction of the finer arterioles controlling the escape of blood from the arterial reservoirs to the capillaries and veins.

In the individual studied the primary pulse waves in the brachial artery supplied almost as much blood to the arm as could escape into the capillaries during a complete pulse period. Consequently the flow in the brachial was almost *nil* except at the time of the primary wave. When the individual was chilled and the flow through the finer arterioles markedly lessened the pulse rate was slowed somewhat and the brachial artery also constricted (see table). Chiefly on account of the reduction in the size of the primary pulse wave the general form of the pulse remained the same, there being an abrupt primary wave followed by a stationary period. Under certain circumstances, however, more blood may enter the brachial artery at each pulse wave than escapes through the periphery during the whole of the pulse cycle. Under such circumstances there is of necessity a backward flow in the brachial artery during the period following the primary pulse wave. This surplus blood probably flows to other portions of the great arterial tree, where the outlets into the capillaries are more free. When the individual is in a warm room and the blood flow in the arm is markedly increased the primary wave in the brachial is far from sufficient to supply all of the blood passing into the capillaries. Consequently the rapid flow in the brachial continues throughout all portions of the cycle.

Nitroglycerin in medicinal doses of one or two drops of the 1 per cent. solution produces very characteristic changes in the pulse form as studied by our method. The primary wave is increased in height (see table), and the smaller secondary waves

are obliterated, leaving only the well-marked dicrotic wave. At the same time the blood flow through the arm is not materially affected. We interpret these changes as being due to a relaxation of the larger arteries of the arm without a corresponding effect upon the arterioles. The large primary wave of the nitroglycerin pulse is nearly always followed by a very marked negative wave, and this in turn by the dicrotic wave. The negative wave is, we believe, due to a reflux of blood which has entered the relaxed artery in excessive quantity and finds no immediate egress through the arterioles.

We have also studied the pulse form in a few cases of aortic insufficiency. In this condition the primary wave is unusually large, and frequently exceeds 2 c.c. in height. It differs from the pulse of nitroglycerin, however, for there is not the same reflection of the primary wave, and, furthermore, the smaller secondary waves are well preserved. These differences are probably due in the main to differences in the condition of the vessel walls, possibly also to differences in the character of ventricular systole. As might be expected, there is frequently a retrograde flow of blood in the artery following the main pulse wave, but we do not regard this as pathognomonic of aortic insufficiency, for, as stated above, it may also occur in other conditions.

STUDIES IN EXPERIMENTAL PNEUMONIA

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The pneumococcus is conceded by all to be the cause of pneumonia in man, but the experimentum crucis, the reproduction of the same disease in animals, has not been made. Wadsworth succeeded in producing bronchopneumonia in rabbits by a preparatory immunization against virulent cultures. Lamar and Meltzer have come nearer than any other experimenters in producing a lesion comparable to that found in man. They did this by means of an ingenious method of intrabronchial insufflation, which, however, does not duplicate the conditions under which the human body becomes infected. We have repeated their experiments in eleven dogs and have succeeded in producing pneumonia in seven, the four failures being probably due to using a catheter with a lateral instead of a terminal opening. We are, however, not convinced that the process induced in the animals can be called lobar. It appears to us that in our cases at least we had to deal with a confluent lobular bronchopneumonia.

Lungs removed as early as one-half hour after intrabronchial injection of living pneumococci show active hyperemia and beginning edematous infiltration of the involved areas. In twenty-four hours consolidation is complete, the lung being solid, airless, and dark red in color. The whole of one lobe is never involved. In thirty-six to forty-eight hours the pleural involvement is more marked, and in seventy-two hours resolution has often begun. In a week to ten days the lungs have almost, if not completely, returned to a normal condition.

Histologically, the alveoli are found encircled by congested capillaries and filled with edema within a half-hour after injection. The alveoli surrounding the bronchi are filled with epithelial cells and mononuclear and a few polynuclear leukocytes. In twenty-four hours the alveoli are full of exudate composed largely of polynuclear leukocytes, a few mononuclears, and epithelial cells. Fibrin is as yet inconspicuous. In seventy-two hours evidence of resolution may be noted. Many of the polynuclear cells show signs of degeneration; the mononuclear cells still predominate, and evidences of fibrin formation are now more apparent.

In this connection it is interesting to note that dogs do not, as a rule, suffer with croupous pneumonia. In them the process is usually lobular in type. The lesions show the presence of more fibrin and less evidences of mononuclear infiltration.

The success of the method, as Lamar and Meltzer have stated, seems to be due to a blocking of the finer bronchioles and thus converting their termini into closed cavities. An analogous condition may prevail in the human subject when the pneumonia is secondary to a bronchitis. In the absence of bronchitis, and such absence is the rule, any other swelling of the bronchial mucosa might act similarly in producing closed cavities. Such swelling might be due to nervous influences, to vasomotor changes, or to anaphylactic phenomena. That the nervous system has an influence in the production of lobar pneumonia has been maintained by a number of authorities, but proof is difficult to produce. Section of the pneumogastric nerve if it leads to pneumonia at all leads to inspirational bronchopneumonia. The vasomotor relations of the lung are but poorly understood. The work of Rosenow, of Chicago, suggests the thought that pneumonia may occur in a given individual because of a previous sensitization with pneumococci present in the mouth or upper air passages. We thought that we might be able in some way to sensitize animals and then by reinfection with pneumococci to produce lobar pneumonia in them. To this end we administered intravenously in dogs and rabbits extracts of pneumococci and pneumococci themselves, and injected the animals intravenously after an interval of twenty-one days with pneumococcus extract. In no instance did anaphyl-

actic phenomena develop, showing that no real sensitization had been produced. In a second series the animals received pneumococcus extract subcutaneously, and three weeks later living cultures of pneumococci. No primary toxic symptoms developed, and aside from a few areas of collapse the lungs at autopsy were found normal. In a third series, after similar preparation, the animals received intrabronchial and intratracheal inoculations, with the same result as in animals that had not been previously sensitized. With the kind coöperation of Dr. R. M. Pearce an attempt was made to discover whether retention of pneumococcus protein could be demonstrated in the lungs of experimental animals. Such a demonstration might have an important bearing upon the local lesions of pneumonia. Without detailing the experiments, which are given at length in our paper, suffice it to say that there is not deposited in the lungs of the rabbit sufficient pneumococcus protein to sensitize guinea-pigs.

In an endeavor to obtain some light upon the crisis of pneumonia, that remarkable and baffling phenomenon, we made another series of experiments, of which we wish to make a preliminary report. We injected rabbits subcutaneously with extract of normal lung, extract of lung in the stage of red hepatization, and extract of lung in the stage of gray hepatization. Sixteen days later the animals were reinjected, this time intravenously, with the same material with which they had been sensitized. Those receiving the normal lung and red hepatized lung died in every instance of anaphylactic shock in five or six minutes. Those receiving extract of gray lung became ill, but recovered without exception within ten minutes. Though we have speculated upon this interesting phenomenon, we have at present no theory to offer, but hope to continue the investigation.

We wish to express our thanks to Drs. Allen J. Smith and R. M. Pearce for their helpful interest in our work.

DISCUSSION

Dr. S. J. Meltzer: The results of Drs. Riesman and Kolmer differ in two points from those obtained by Lamar and myself with the method of intrabronchial insufflation. Riesman and Kolmer produced pneumonia only 7 times in 11 experiments. Lamar and I obtained 42 times in 42 experiments; that is, we produced pneumonia in every experiment. Further, Riesman and Kolmer, who, like Lamar and I, employed a culture of a virulent pneumococcus, state, if I understood them correctly, that in their experiments the pulmonary lesion was of a bronchopneumonic type, while in our experiments the lesion was in every case of a classical fibrinous form of pneumonia. The reason for these differences may perhaps be found in the fact that we have employed a tube with an opening only at the end of it which compelled the bouillon culture to enter only into one end bronchus, while Riesman and Kolmer employed a catheter with side openings which permit the scattering of the culture over larger areas and various lobes, thus either being insufficient to produce a pneumonic lesion in any place or producing several foci and thus giving the impression of a bronchopneumonic lesion.

Dr. A. B. Wadsworth: I have had experience in the last five or six years with the induction of pneumonia in dogs, and like Dr. Meltzer, I have been unable to determine any fundamental differences in the dog lesions as compared with those of man. Bezzola and Ribbert[1] called attention to the fact that even in the diffuse lobar pneumonias of man there is a lobular structure to be distinguished in the arrangement of the fibrin, the exudate cells, and the pneumococci within the lobule. This is quite characteristic, and is apparent in the early stages of uniformly diffuse lesions and in the lobar pneumonias which are obviously patchy.

In the induction of pneumonia in dogs I used at first a method practically similar to Dr. Meltzer's, but lately I have substituted the stiff Mercier catheter, because I could introduce it through the vocal cords more readily than the soft rubber ones. This catheter is passed down into the lung before injecting the fluid. I pass it beyond the bifurcation of the trachea so that I can feel assured of reaching a definite part of the lung. The Mercier catheter has an opening on the side, but I think the principle of the method is very much the same as that of Dr. Meltzer's in that a considerable quantity of fluid must be injected in order to secure typical lesions—a portion of the lung is flooded. It is important to have a virulent culture and a large quantity, as the dog is an extremely resistant animal.

[1] Virchow's Archiv, 1894, vol. cxxxvi, pp. 305 and 359.

Dr. J. J. Kinyoun: Some sixteen years ago this subject of pneumococcal infection was studied by Dr. Rosenau, who was in charge in the Hygienic Laboratory in Washington. I was in association with him and asked him to speak of his work here, but he declined, therefore I am going to speak for him. The results of the experiments on the pneumococcus were published in the Report of the Surgeon General. In the experiments in our attempts to induce lobar pneumonia a certain percentage of the dogs yielded both clinical and pathological findings of this disease, and it is just as Dr. Meltzer has said, that it was produced by considerable quantities of pneumococcus culture by a catheter.

Dr. Riesman: In following the cases from day to day we have not found that an entire lobe was involved at the start. While histologically the disease bears a strong resemblance to human pneumonia, its mode of spread—one of progressive invasion—is different from the simultaneous massive involvement of an extensive area characteristic of pneumonia in man.

A CONTRIBUTION TO THE SYMPTOMATOLOGY OF THROMBOPHLEBITIS IN TYPHOID FEVER

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EVERYONE who sees any considerable number of typhoid fever cases year after year must have been struck with the fact that while most of these run a fairly typical and uneventful course, there is a considerable group of cases in which the latter part of the course, or the period of convalescence, is marked by a number of obscure and apparently unrelated symptoms and complications. If one takes the trouble to read over a large number of case histories and charts of typhoid this fact is brought out even more clearly and forcibly; for many of these incidents are so transient and apparently insignificant that they fail to make much impression and are readily forgotten.

These symptoms include various forms of irregular febrile movement; sudden pulmonary and pleural symptoms; sudden and unaccountable abdominal symptoms; repeated chills, without obvious cause; pain, discomfort, and stiffness in the legs or arms; pain in the heel; tenderness of the toes, etc. In some, but by no means in all, of these cases frank signs of thrombophlebitis* appear at some time in the course of the illness.

It is my purpose in the present paper to attempt to show that many or most of these obscure late interruptions of the normal

*In the present article the terms thrombosis and phlebitis are used interchangeably and without distinction to denote the whole process included in the longer term thrombophlebitis, and no attempt is made to settle the still uncertain and much discussed question as to whether the formation of the thrombus or the inflammation of the vein wall is the primary process. The weight of evidence at present, however, seems to favor the view that thrombosis occurs first.

course of typhoid have a common underlying cause and that this cause is thrombophlebitis.

Before considering the individual symptoms it will be necessary to call attention to certain facts concerning phlebitis itself as it is seen in typhoid fever.

Thrombophlebitis Probably a Much More Frequent Complication than is Commonly Supposed. In most writings upon the subject the incidence of this complication of typhoid is placed at about 2 per cent. In 829 cases studied by Osler[1] the percentage was 1.9. In Thayer's analysis[2] of 1463 cases venous thrombosis occurred in 2.6 per cent. My own belief is that these figures do not begin to represent the actual frequency of this complication. Among 1540 cases of typhoid treated in the New York Hospital between 1898 and 1912 there were 78 instances of undoubted venous thrombosis (5 per cent.). If to this number be added the cases in which no thrombosis was recognized, but which presented other symptoms, that, as I hope to show, are usually indicative of the existence of a latent thrombosis, the percentage is increased to 8 or 9. Da Costa[3] reports that in a series of 135 soldiers treated for typhoid in the Pennsylvania Hospital during the Spanish American war the complication of milk-leg occurred 16 times, or in nearly 12 per cent. Vincent,[4] in a group of cases studied by him, found the complication of phlebitis in 8.23 per cent.

It is my conviction that the further study of this complication in its various phases, and especially the more prompt recognition of its milder and less characteristic manifestations, will show that venous thrombosis occurs in from 10 to 15 per cent. of all cases of typhoid fever.

The Development of Thrombophlebitis is Gradual and its Classical Symptoms Appear only Late in the Process. The recent beautiful histological studies of Aschoff[5] show that the formation of the primary white thrombus is due to the gradual deposit, layer upon layer, of blood platelets, while the blood is still flowing in the affected vein, in a manner somewhat comparable to the formation of a bar by the gradual deposit of silt in a flowing stream. The complete occlusion of the vein is a late phase of this process. The symptoms by which thrombophlebitis is ordinarily recognized

—edema, pain, tenderness and periphlebitic induration—are seen usually only after such occlusion has occurred, for not until then do the signs of inflammation of the vein wall, and especially of the surrounding tissue, become pronounced. Up to that time the process of thrombosis either runs a latent course or manifests itself by symptoms so mild or so little characteristic that they are apt to be overlooked or misunderstood. Vaquez,[2] in his admirable study of phlebitis, lays stress upon the fact that this process need not result in complete occlusion of the lumen of the vein, and adds that "to wait until there is a total obliteration before saying that, clinically and anatomically, there is a phlegmasia alba dolens is an error analogous to that made by waiting for the existence of pulmonary cavities in order to diagnosticate tuberculosis."

That extensive thrombosis of the veins of the extremities may develop without giving recognizable symptoms has often been demonstrated by the postmortem examination of patients dying of pulmonary embolism. The obstetric, gynecologic, and surgical literature abound with such instances. Vaquez,[6] in discussing the phlegmasia alba dolens which declares itself during the convalescence of typhoid, insists that the process itself often begins insidiously and latently long before the symptoms appear. In support of this statement it would be easy to cite many instances from among the typhoid cases included in this study if space permitted.

The Thrombotic Process in Typhoid Tends to be Much More Extensive and Widely Disseminated than the Symptoms Would Seem to Indicate. One of the points brought out clearly in the present study is that the thrombosis is usually widely scattered and extensive even when the frank symptoms of the trouble may be quite circumscribed. For example, there may be slight pain, or muscular soreness, or points of tenderness in both calves and feet and then, some days or weeks later, distinct signs of phlebitis—*i. e.*, marked tenderness and periphlebitic induration—only over a small area of one femoral vein. In other cases there will be frank signs of phlebitis only in one leg or thigh, and yet, some weeks later, after the patient has been permitted to get up, there will be marked edema of *both* legs. Not so very infrequently, in addition to phlebitis of the leg veins, there will be pain and more or less tenderness of one or the

other arm. In one woman there was, in addition to phlebitis in both legs, distinct involvement of the veins of first one and then the other breast. Occasionally the process will seem to be confined chiefly to the small superficial veins, and will show a tendency to migrate from spot to spot over the legs, buttocks, and lower part of the trunk.

THE PULMONARY COMPLICATIONS OF THROMBOPHLEBITIS

Although it is well known that pulmonary embolism is an occasional complication of venous thrombosis, attention has been centred chiefly upon the large, fatal emboli which, while fortunately rare, are yet so dramatic in their occurrence and so tragic in their results as to leave a deep impression when they do occur. Such emboli usually result from the separation of a fragment from a thrombus occupying and occluding some large vein, such as the femoral or iliac. They therefore are apt to occur late in the course of the phlebitic process. But there is another and much commoner type of pulmonary embolism which differs radically from that just referred to in its time of occurrence, clinical course, and prognosis, and which has received far less attention than it deserves.

As a result of some personal experiences with this latter type I published recently a short paper[7] calling attention to the comparatively frequent appearance of small pulmonary emboli in the course of venous thrombosis, and especially to the fact that such emboli in many cases make their appearance a number of days, or even two or three weeks, before any signs of thrombophlebitis can be detected. In 7 of the 9 cases reported the thrombosis had occurred in the course of typhoid fever. It seemed to me, therefore, that it might be instructive to go over the records of a large number of cases of typhoid with a view to ascertaining (1) what proportion of these cases complicated by phlebitis showed evidences of such pulmonary embolism, and (2) what proportion of the pulmonary and pleural complications of typhoid could reasonably be ascribed to pulmonary embolism and infarction. With these points in mind the records of all cases of typhoid treated in the New York Hospital between 1898 and 1912, in which the complications of

phlebitis, pneumonia, or pleurisy were recognized, have been carefully analyzed, and the results of this analysis form the basis of this paper.

Among the 1540 cases of typhoid there were 88 with pulmonary or pleural complications, exclusive of bronchitis. Among the 88 cases there were 25 (28 per cent.) in which the thoracic complications were almost certanly *not* of embolic nature. (These 25 cases formed a group having a strikingly uniform and sharply defined clinical picture. Almost without exception the pulmonary symptoms appeared early in the disease and began as a severe general bronchitis. This grew progressively worse, and sooner or later resulted in bronchopneumonia, which was usually double, and which usually involved the greater part of both lower lobes. Seventeen of these cases terminated fatally.)

There are 8 cases (9 per cent.) complicated by phlebitis which showed, at some time, pulmonary symptoms, but these symptoms were either not sufficiently characteristic or the records not sufficiently complete to warrant their being included among the cases of pulmonary embolism. Some of these cases, however, were almost certainly of this nature.

There were, further, 26 cases (30 per cent.) in which the character of the thoracic symptoms made it seem very probable indeed that they were instances of pulmonary embolism, but in which the records furnished no other evidence of thrombophlebitis. Finally, there were 29 cases (33 per cent.) in which there were frank signs of phlebitis, and in which the pulmonary or pleural symptoms could be assumed with reasonable certainty to be due to embolism and infarction.

Among these 29 cases of pulmonary embolism 19 gave their symptoms of this condition before the phlebitis had declared itself and 10 after the signs of phlebitis had appeared.

The above figures may be tabulated thus:

	Cases.	Per cent.
Pulmonary and pleural complications (exclusive of bronchitis)	88	
Pulmonary embolism before appearance of phlebitis, 19; pulmonary embolism after appearance of phlebitis, 10	29	33
Phlebitis with pulmonary symptoms of doubtful nature	8	9
Probable pulmonary embolism without evident phlebitis	26	30
Pulmonary complications not embolic	25	28

The evidence upon which is based the conclusion that a very large proportion of the pulmonary and pleural complications of typhoid are embolic in nature is and necessarily must be chiefly circumstantial. Such emboli are almost small; the cases rarely die, and none of our cases has come to autopsy. Since the evidence is largely circumstantial its force depends upon the accumulation and massing of it. It has therefore seemed to be necessary to record, in condensed form, all of the case histories. Whoever has the patience to read through these, case after case, will be likely to recognize a fairly distinct clinical picture, and in reading the cases of probable embolism without evident phlebitis will be convinced, I believe, that most of them are really cases of embolism.

The character of the records of the medical service of the New York Hospital probably does not differ materially from that of records of other hospitals of the same class. They have the failings inherent in a system which places chiefly upon the often overworked interne staff the responsibility for the proper recording of the progress of the patients and of most of the daily events of the wards. These failings are usually chiefly sins of omission. Many transient and apparently unimportant symptoms, which may have been promptly recognized and properly cared for, are yet not noted in the permanent records of the patient. It is reasonable to assume, therefore, that the records of the cases under consideration sometimes fail to include facts that might have served to identify a mild phlebitis or a small pulmonary embolism, and that the figures as given above, if they err at all, do so on the side of conservatism.

SYMPTOMS OF PULMONARY EMBOLISM AS SEEN IN TYPHOID FEVER

As has been said already there are two quite distinct types of pulmonary embolism. In one the embolus is large; the attack is violent and usually fatal, and the symptoms, as a rule, appear only late in the course of the phlebitis. In the other the embolus is small, the symptoms are often very mild and transient, the prognosis is good, and the attack, in a majority of the cases, occurs some days before any of the usual symptoms of phlebitis can be

discovered. The first type is rare; the second is relatively common. In the latter type the character of the symptoms and the time of their occurrence make it highly probable that these small emboli are derived from the freshly forming and friable mural thrombus before it has occluded the vein and while the blood is still flowing past it. That is the time when the thrombosis usually gives no local symptoms and the time also when one would naturally expect small particles to be carried away into the venous blood stream. Indeed it is difficult to conceive of the gradual formation of a thrombus, by the deposit of blood platelets upon the wall of a still patent vein, without some fragments being washed away and ultimately deposited in the lung capillaries; and one is inclined to wonder, not at the frequency of embolism in the early stages of thrombosis, but rather that a case of thrombosis should ever run its course without such early pulmonary emboli.

The observation that phlebitis may give rise to pulmonary embolism long before it manifests itself by local symptoms is by no means a new one. Vaquez,[6] in describing various modes of onset of phlebitis, speaks of one under the caption "Phlébite latente à début embolique." Such patients, in the course of some affection likely to be associated with phlebitis, suddenly feel a stitch in the side followed by a little fever, sometimes with some bloody sputa. The trouble, which may be ascribed to an intercostal neuralgia or to a slight focus of congestion, rapidly disappears; then sometimes the same phenomena are repeated two or three times. Finally eight, ten, or fifteen days afterward a phlebitis suddenly appears in one of the extremities.

Vialard[8] reports four examples of early pulmonary infarction in phlegmasia alba dolens. A number of such instances can be found also among the cases reported by Mahler[9] and by Zurhelle.[10]

An analysis of the cases cited by Osler[1] in his exhaustive "Studies in Typhoid Fever" shows this same association of obscure pulmonary and pleural symptoms with phlebitis. For example, Case No. 13813 is cited among the cases complicated by pneumonia and also among those complicated by phlebitis. Cases Nos. 17319 and 18156 are mentioned under the heading of the complication of pleurisy and under that of phlebitis. Case No. 13524 appears under

the three groupings of "painful legs," pleurisy, and post-typhoid elevation of temperature.

An analysis of the 29 cases of pulmonary embolism occurring with known phlebitis shows that *thoracic pain* was present at some time in almost every case. In a majority of the cases it was the first symptom noticed. The pain was usually sudden, sharp, and severe, and was felt commonly in the lower part of one or the other axilla. Occasionally it was referred to the hypogastrium, the shoulder, or the lower part of the neck. The duration of the pain varied from a few hours to a number of days. *Cough* was present in most but not in all cases. In eight instances it was the first symptom. Sometimes it did not appear until two or three days after the onset of the pain.

Bloody sputum was noted in 13 (45 per cent.) of the cases. It sometimes appeared promptly, but frequently was seen only several days after the onset of the attack. Often the blood-spitting continued for many days. The blood was raised usually in small clots or streaks. At the onset such sputa are usually bright red; they soon become dark, however, and if the spitting continues for many days the altered blood gives a brownish color to the sputum. True rusty sputum was never seen.

Sudden *thoracic oppression* and *dyspnea* were present at the onset of the attack in only 3 cases. In 5 instances the pulmonary attack was introduced by one or more *chills*. The behavior of the *temperature* varied much. In some cases it rose abruptly with the advent of the thoracic symptoms, but often it was not easy to determine whether the variations in the temperature were to be ascribed to the phlebitis, to the embolism, or to the primary disease.

Rigidity of the upper portion of the abdominal musculature, and tenderness just below the ribs were present in several cases in which the infarction seemed to be situated at the diaphragmatic surface of the lung.

Multiple Embolism. In 13 of the 29 cases the symptoms were such as to indicate the occurrence of two or more attacks of pulmonary embolism. Among the cases of probable embolism without signs of phlebitis there were 5 in which the multiple character

of the pulmonary attacks leaves little room for doubt as to their true nature. In one of these (Case 39) there were four distinct attacks during a period of three and a half weeks.

Fatal Embolism. Death occurred in 3 of the 29 cases of pulmonary embolism with recognizable phlebitis (Cases 22, 27, 28). In each instance the fatal attack occurred late in the course of the phlebitis and had been preceded by milder pulmonary attacks.

Physical Signs. As regards their physical signs the cases may be divided into three groups:

1. Those in which friction rubs or crepitant rales over a small area were the only signs. These signs often lasted only two or three days.

2. Cases in which the signs were those of a small, circumscribed pneumonia. The area of consolidation did not extend, and in each instance the signs of consolidation disappeared within three or four days. These signs were almost always in the lower lobes.

3. Cases with signs of extensive plastic pleurisy or of pleural effusion. This type included more than half of all the cases. In some of these the physical signs at first were those of consolidation. It seemed to be quite characteristic of the third group of cases that although the signs seemed to indicate the presence of liquid, exploratory puncture usually failed to reveal it. In only three cases was serum obtained and in only one of these was there any considerable quantity.

PULMONARY EMBOLISM BEFORE THE APPEARANCE OF SIGNS OF PHLEBITIS

Case 1.—D. R. D., male, aged thirty-two years. No. 1373. Admitted October 23, 1898, on ninth (?) day of illness. On this day patient developed a troublesome cough. On the next day (October 24) the sputum was blood streaked. October 26, "patient raised quite a considerable amount of blood." The cough and bloody sputum lasted for several days. On November 6, there was pain in the left groin and leg and, two days later, "tenderness in calf and along course of the long saphenous vein." Later still the leg became edematous. The temperature, which had been normal, rose for two days with the appearance of the signs of phlebitis.

Case 2.—W. B., male, aged twenty-six years. No. 2806. Admitted August 31, 1899, on ninth day of disease. Five days later (September 4) patient had a chill at noon and three hours later became very cyanotic, vomited, had a rapid, weak pulse and began to cough up blood streaked mucus. September 12, had chill and became cyanotic. September 13, two chills. Over lower part of right chest behind, dulness, broncho-vesicular breathing, and crepitant rales. September 14, "patient cyanotic; pulse very weak." During the next three days several chills. September 19, pain in right leg. September 20, signs of fluid over lower part of right chest behind. Pain, tenderness, and swelling appeared in right thigh and calf. On September 27, pus was evacuated from right thigh, and on October 12, pus was discovered in right calf. Later there developed pain, tenderness, and redness along the lower part of the inner side of the leg which persisted for a fortnight or more and gradually disappeared. The chest signs slowly disappeared and the patient recovered.

Case 3.—M. B. W., female, aged twenty-four years. No. 2987. Admitted October 12, 1899, on fifth (?) day of illness. Severe course with persistent nausea and vomiting. October 17, patient had a chill with sweating and soon afterward began to have severe abdominal pain. On the following day the pain was very severe and was localized over the right side of the chest. October 23, pain appeared in left leg and popliteal space. October 27, pain in left side of chest. October 29, pain began in *right* leg. November 2 and 4, chills. Pain in legs continued and on November 11 there was tenderness along the course of the femoral vein in both thighs. On the evening of November 17 there was a chill followed by sudden, severe pain referred to the region of the right shoulder, and the patient was delirious through the night. All the symptoms gradually subsided and the patient recovered.

Case 4.—D. P. T., male, aged twenty-four years. No. 6593. Admitted November 23, 1901, on twenty-first day of illness. The patient was delirious and very sick. Over the left lower lobe there was on admission, dulness, diminished breathing, and subcrepitant rales. On November 28 there was bronchial voice and breathing at the level of the angle of the scapula and signs of fluid below this. November 29, "area of consolidation unchanged. Signs of fluid much less." December 3, "pain and tenderness along course of both internal plantar nerves." This pain in soles of feet was troublesome for some days. On the night of December 16, patient developed a troublesome cough and, on following day, began to have very severe pain in right side of chest and in right shoulder, and the temperature rose from 100° to 104° F. The pain and cough continued through the night, and next day over the right lower lobe there were signs of fluid, and that evening 25 ounces of clear fluid were removed. December 23, "patient complaining of pain in right leg and groin for several days. Tenderness

is very marked over veins of thigh, where a cord can be felt." The phlebitis ultimately subsided without edema.

Case 5.—M. M., male, aged eighteen years. No. 8179. Admitted September 21, 1902, on fifth day of illness. Ran a fairly severe course. No pulmonary signs or symptoms on admission. September 27, at 5 P.M., began to have very severe pain over left lower chest and in epigastric region and temperature rose to 105.8° F. Patient was delirious much of the time for several days. No definite signs in the chest. October 11, "has improved very much. Mind quite clear. Complains of pains in left thigh and there is slight tenderness along course of the femoral vessels. For several days patient has been complaining of painful feet and his toes are very tender." October 13, "complains of left arm being painful and is unable to bend elbow." November 15, tenderness along course of femoral vein had disappeared, but toes still somewhat tender. Good recovery.

Case 6.—W. C. C., male, aged forty years. No. 8467. Admitted November 17, 1902, on ninth day of illness. Very severe course; delirious much of time. November 21, sudden pain in left chest, followed by coughing. November 22, at 3 A.M, sudden cyanosis and dyspnea. Dyspnea continued throughout day. Troublesome cough. During next three weeks much coughing and frequent sweats. Beginning December 12, frequent chills and sweats. December 15, severe pain in right leg followed by signs of phlebitis in thigh and leg. December 20, pain in right chest and great restlessness. More cough. December 26, signs of phlebitis in left calf. Return of pain in right chest. January 4, small area of dulness and a few crepitant rales in (right?) lung. Sputum streaked with blood. January 5, patient developed signs of edema of the larynx and died, in spite of a tracheotomy.

Case 7.—J. D., male, aged twelve years. No. 9879. Admitted September 6, 1903, on fourth day of illness. Ran severe course. September 13 and 14, intestinal hemorrhage. September 21, area of dulness near angle of right scapula with bronchial breathing and voice and many coarse rales. The cough and signs of consolidation lasted several days. September 27, complained of pain in left leg, most marked along inner side of thigh where there is tenderness but no cord to be felt. Next day the temperature rose and continued high for some days. October 1, "consolidation clearing up. Toes of both feet are tender." October 5, toes no longer tender, and tenderness along inner side of thigh has disappeared. No further symtoms.

Case 8.—R. A. R., male, aged twenty-seven years. No. 10130. Admitted November 14, 1903, on tenth day of disease. Ran a moderately severe course. Lungs normal on admission. November 16, right wrist painful and tender. November 21, during the night there was sudden

severe pain in right side, requiring anodynes. The pain continued through the day, without physical signs. November 25, "abundant fine pleuritic rales in right axilla and at right base." The pains and the signs of plastic pleurisy continued for several days. The pain, tenderness and redness of right wrist also continued and extended to the palm of the hand. December 5, "right wrist and hand not swollen but still somewhat tender. Today there is pain and tenderness in the left popliteal space and the left calf is somewhat swollen." Later the thigh became swollen and tender along the course of the femoral vein and a tender cord could be felt in the popliteal space.

Case 9.—J. M., male, aged eighteen years. No 14283. Admitted to hospital August 31, 1906, on fifteenth day of illness. Severe course. Slight cough on admission. "Lungs normal except for a few scattered rales." September 2, chill at 4 P.M. with rise of temperature to 105.6° F.; at 8 P.M., a second chill, temperature 106.6° F., respiration 36, pulse 124. September 3, chill at 8 A. M. and again at 7 P.M. No cough, pain or expectoration noted. September 5, chill. September 6, pain referred to left shoulder. Slight resistance and tenderness in left upper quadrant of abdomen. Chill at 11 P.M. September 7, chill at 7.30 A.M. Severe pain in left chest, relieved somewhat by strapping chest. September 8, "patient has had three attacks of severe pain in left side, each time accompanied by profuse sweating. Many fine crepitations over left lower back and in left axilla, brought out after coughing." September 11, pain gone. Signs of fluid over lower half of left chest, but needle, inserted in two places, revealed no fluid. September 12, chill at 6 P.M., temperature 106.4° F., respiration 40, pulse 140. September 14, chill at 6 P.M. September 17, temperature normal. "At left base, dulness, diminished fremitus, a few rales and soft bronchial breathing." On September 18, 19, and 20 some elevation of temperature without apparent cause. September 23, temperature up. Pain in left groin and tenderness from groin down inner side of thigh to popliteal space. September 24, cough more troublesome. "Is raising bloody sputum today." Some dulness with diminished breathing and voice at right base. The signs of phlebitis in the left thigh and leg lasted for some time. The leg became edematous and some weakness and foot drop were noticed when the patient attempted to walk. The patient made a slow but complete recovery.

Case 10.—J. M., male, aged twenty-eight years. No. 14943. Admitted February 18, 1907, on the fourteenth day of illness. Patient had a dry cough on admission and, on evening of the same day, spat up considerable bloody sputum. February 22, "marked dulness over entire right lower lobe, diminished breathing and many crepitant and subcrepitant rales." Cough and bloody sputum continued for some days. February 25, pulmonary signs unchanged. Sputum had become foul smelling and dark

in color. A needle inserted in lower part of right chest behind, withdrew thick, dirty red, foul smelling material. The signs of a gangrenous abscess in the lung gradually subsided and the temperature fell to normal. On March 15, patient sat up for first time. March 20, marked signs of phlebitis in both legs; severe pain, tenderness, and edema. Gradual recovery.

Case 11.—S. B., male, aged thirty-four years. No. 15227. Admitted April 14, 1907, on twenty-first (?) day of disease. On April 16 and 17, there are notes of abdominal pain and rigidity but the position of the symptoms is not given. April 21, "pain in the right side on breathing or coughing. A few friction sounds in right axilla. Below angles of right scapula there is dulness and diminished breathing." April 24, right chest aspirated, 175 c.c. of clear fluid obtained. April 27, "sputum brownish red." April 30, "sputum still bloody and foul smelling." On May 8, a needle inserted into right chest posteriorly revealed pus and patient was transferred to the surgical service and operated upon for a pulmonary abscess. Patient was allowed up on June 9, and two days later there were signs of phlebitis in both legs with marked edema. Slow recovery.

Case 12.—J. S., female, aged thirty-five years. No. 15687. Admitted to hospital July 30, 1907, on thirteenth day of illness. Ran a moderately severe course, the fever gradually falling, so that on the twenty-second day (August 8) the temperature remained below 100° F. On August 9, at 8 A.M., patient had a normal temperature and felt well. At 8.40 A.M. she complained of acute pain in the region of the heart, became cold and blue, and broke out in a cold sweat. She complained of three such severe attacks of pain within an hour. The pulse rose from 72 to 116, the respirations from 20 to 44, and the temperature from normal to 103.6° F. During the afternoon and evening there were frequent paroxysms of pain in left chest, the patient was cyanosed and cold, the pulse rapid and feeble. There was also ridigity of the upper part of the left rectus muscle, with tenderness. During August 10 and 11 there was troublesome dry cough with more or less pain in left chest. Pleuritic friction sounds could be heard in the left axilla, and there was a distinct pleuropericardial rub. August 12, "patient still somewhat cyanotic. Dry cough and pain in left axilla still persists." August 13, cough accompanied by blood-stained expectoration. Impaired resonance, feeble breathing, and many crepitant rales at right base posteriorly and many crepitant rales in left axilla. August 14, "sharp pain in right side of neck and right shoulder. Troublesome cough but no expectoration." August 17, dull ache in left thigh and groin which next day extended to left calf. August 19, sudden stabbing pain in right chest. August 20, expectoration of bright blood which continued for several days. On August 26 there developed pain, tenderness, and

swelling along the course of the right femoral vein; the tenderness extended up along the course of the external iliac vein, and there was swelling and tenderness of the labium major on that side. August 30, pain referred chiefly to sole of right foot. Later edema appeared in both legs. The chest signs gradually cleared up and patient made a good recovery.

Case 13.—Mr. H., aged fifty years. Admitted September 2, 1910, on second day of illness. Course mild and uneventful until September 19. He then developed a troublesome cough to which was added, on September 22, pain in left side of chest, which for a day or two was very severe. On the night of October 6, he had a chill and, a few hours later, severe pain in the left scapular region and cough. The pain and cough lasted for some days. On October 10 he spat up some bright blood-streaked mucus and for several days afterward the sputum contained dark blood. On October 15 he began to have pain and tenderness in right leg which, two days later, extended to the thigh along the course of the femoral vessels. On October 26 the same symptoms appeared in the left leg and about the same time he suffered greatly for several days with pain in the lumbar portion of back. The phlebitis in both legs ran a long and severe course. The temperature, which had reached normal, rose abruptly on October 7 after the chill and continued high and irregular throughout the course of the phlebitis.

Case 14.—L. C., male, aged twenty-nine years. No. 20379. Admitted September 9, 1910, on sixth day of disease. Mild course; uneventful until September 21. Then sudden severe pain referred to right hypochondrium, rapid breathing, and rigidity of upper part of right rectus muscle. That evening "many crackling pleuritic rales in right axilla." One week later "slight tenderness along inner side of right leg." No further notes on the condition of the legs. Discharged October 22. A few days later friends of the patient reported that he had "swelling of both legs below the knees."

Case 15.—F. Z., male aged thirty-two years. No. 20513. Admitted October 3, 1910, on ninth day of disease. Uneventful and rather mild course until October 22 when he complained of pain in left axilla and had "a few fine pleuritic rales" in the same region. On the next day the entire left leg seemed slightly swollen, was bluish in color and there was marked tenderness over the femoral vein. October 24, "marked tenderness in abdomen just above left Poupart's ligament." October 29, tenderness in *right* thigh. November 1, "pleural friction rub low in left axilla." When discharged there was still some edema of left leg.

Case 16.—H. C. B., male, aged twenty-one years. No. 20632. Admitted October 25, 1910, on the eighth day of disease. Ran a moderately severe course. November 6, in afternoon began to cough severely and continued to do so for a number of days. November 13. Complained of pain in side of chest on breathing. "Low in left axilla and posteriorly over left

lower lobe, are scattered coarse friction rubs." November 22 to 26, intestinal hemorrhages. The temperature, after having been normal for two weeks, rose abruptly on December 7 and continued fairly high for a fortnight or more. On December 11 signs of phlebitis appeared in the right thigh and later showed also in the right calf. There was no edema.

Case 17.—Mrs. L., aged forty-three years. Admitted December 18, 1910, on about the tenth day of disease. Moderate initial course followed by equally long "relapse." For about one week, beginning on December 24, patient coughed much and had bloody expectoration. Later a few fine rales could be heard in both axillæ and at both bases behind. On January 22 patient began to complain of pain in left arm. On January 27 pain began in right leg and a few days later in the left leg. The pain was especially severe and protracted in the left leg where there was marked tenderness over the lower third of the anterior surface external to the tibia. At the time of discharge there was still slight edema of the foot and ankle.

Case 18.—A. C., female, aged thirty-seven years. No. 180098. Admitted November 24, 1911, on eighth day of illness. Moderate course. Temperature gradually falling and patient conscious and comfortable when at 9 P.M. on December 4 (eighteenth day) she complained of sharp pain in left side of chest. The pain continued next day but the signs in the chest were negative except for many fine rales at the end of inspiration. Patient spat up a small amount of bright blood. December 7, "still spitting up a small amount of bright blood occasionally. Still no definite signs in chest." No pain or tenderness along course of veins of legs. December 8, still coughing. In morning complained of pain in right heel. Later in the day there was slight pain in right knee. "Still no signs of phlebitis." The temperature, which has been below 101° F. for some days, rose in the afternoon to 104° F. and remained high for four days. December 9, slight tenderness over position of Hunter's canal and in popliteal space of right leg. December 12, patient complained of more pain in left side of chest. December 13, cough much worse. Sputum again contained bright blood. Pain in left knee. "No signs of phlebitis on that side." December 14, tenderness over Hunter's canal on *left* side. December 15, severe pain in left side of chest. At left base dulness and many fine rales. The cough and bloody sputum continued for several days longer. The phlebitis of both legs lasted for some time and subsided without edema.

Case 19.—H. P., physician, aged twenty-four years. Onset on June 9, 1910. Moderately severe course which was uneventful until the evening of twelfth day (June 21) when he was awakened by sudden, severe thoracic oppression and a feeling of suffocation. He had dyspnea, cyanosis, cold sweat, a rapid, thready pulse, and all the indications of alarming collapse. On the following day these symptoms had somewhat subsided. Examina-

tion of the chest was negative. June 23, symptoms subsiding. Lungs negative except for diminished breathing and crepitant rales at angle of left scapula. In the afternoon began to have pain in left side of chest which, on following day (June 24), became very severe. Very slight cough. No signs of phlebitis. June 26, began to expectorate mucus mixed with dark blood. June 28, sharp pain in *right* side of chest. June 29, soreness in calf of right leg which, on following day, extended along the course of the femoral vein in thigh. The bloody sputum and cough continued for some days longer. July 5, some pain in left calf. No further symptoms until July 14 when signs of phlebitis in left femoral vein appeared. The signs of plastic pleurisy in the left chest slowly disappeared and patient made a good recovery.

PULMONARY EMBOLISM AFTER THE APPEARANCE OF SIGNS OF PHLEBITIS

Case 20.—W. E. S., male, aged twenty-five years. No. 1572. Admitted December 4, 1898. Typhoid began in Porto Rico on October 8. Improved until November 13, when right leg became tender and swollen. This improved and patient left hospital. Two days before entrance to New York Hospital (December 2) the left leg became swollen and tender in the calf and, on the following day, he had pain in left chest near his heart. On admission there was dulness and diminution of voice, breathing and fremitus at the left base and signs of phlebitis in the left leg. Recovery.

Case 21.—H. W. W., female, aged twenty-five years. No. 2966. Admitted October 7, 1899, on tenth day of illness. Severe course. October 14, pain and tenderness along course of femoral vein in right thigh. Chills on October 17 and 18. October 22, very severe pain in left side which was followed by signs of pleurisy with effusion in left chest. October 23, signs of phlebitis in *left* leg. Later edema of both legs.

Case 22. -J. L. L., male, aged twenty-six years. No. 6393. Admitted October 14, 1901, on sixteenth day of illness. On day before admission began to have severe pain in left thigh and leg and on admission showed well marked signs of femoral phlebitis. October 21, soreness and tenderness in left heel, which lasted several days. October 23, sudden change for the worse, with very rapid pulse and breathing. October 24, pain in right side of chest, with many friction sounds. October 27, chill, with rise of temperature and labored breathing. Over lower part of right chest, flatness and diminished breathing, voice and fremitus. October 30, small amount of fluid obtained from right chest. October 31, signs of phlebitis in *right* leg. Very severe pain and tenderness in foot and heel which lasted some days. November 17, sudden death, due probably to pulmonary embolism. No autopsy.

Case 23.— G. H. C., male, aged thirty-two years. No. 9892. Admitted September 8, 1903, on fourth day of illness. Very severe course. September 14, pain in left popliteal space. September 18, chill. September 23, slight edema of left ankle. Tenderness and swelling of right calf. September 25, severe chill. September 27, chill. Dulness and many crepitant rales at left base posteriorly. September 28, coughing. Two chills. Signs of consolidation at left base more distinct. October 9, still signs of phlebitis in both legs. October 11, two profuse sweats. October 12, chills. Slight dulness and many crepitant rales over upper part of left lower lobe. Sings of fluid at base. Small amount of bloody fluid aspirated.

Case 24.—H. P., female, aged twenty-five years. No. 13748. Admitted April 6, 1906, on seventh day of illness. Long, severe course. April 21, began to complain of painful and tender toes, also of pain in both legs, but especially in left leg. April 23, tenderness in right groin below Poupart's ligament. April 25, cough and expectoration with rales at base of right lower lobe. Between April 26 and May 22 patient had eight severe chills, with fever of markedly remittent type. During most of this time she suffered greatly from tenderness and pain in the toes. May 6, frank signs of phlebitis in left leg and later in thigh. May 22, after a chill patient has a violent attack of coughing and complained of severe pain in left chest. For several days thereafter severe pain in left chest and left upper quadrant of abdomen. Irregular temperature continued for a fortnight longer.

Case 25.—V. A., male, aged forty-two years. Admitted February 8, 1910, on sixth day of illness. Long, severe course. February 19, chill and later pain and tenderness over left femoral vein. Up to that time he had had no cough whatever. That night he was disturbed several times by coughing attacks which ceased next day. February 26, chill, high temperature, and signs of phlebitis of *right* femoral vein. March 5, sudden severe pain in right chest, cough, bloody sputum, dulness, and rales at right base posteriorly. Later signs of consolidation in right lower lobe became more distinct. Cough and expectoration of blood lasted for two weeks. Slight chills with rise of temperature on March 15 and 25. On March 15 patient complained of great tenderness in toes of both feet, which continued several days. Later edema of both legs. No rise in leukocytes.

Case 26.—M. P., male, aged twenty-three years. No. 20284. Admitted August 22, 1910, on eleventh day of illness. Moderate course and uneventful convalescence until September 20. Patient had been up and about ward for several days and on this day temperature began to rise. On the following day there was pain in left thigh but no other indications of phlebitis. Later in the day there developed pain in right side of chest, made worse by deep breathing, and a few friction rubs could be heard in the right axilla. The pulmonary symptoms soon disappeared. All the usual symptoms of femoral phlebitis developed rapidly and lasted for two weeks.

Case 27.—D. C., male, aged twenty-three years. No. 178211. Admitted July 20, 1911, on fourteenth day of illness. He then complained of pain in the calves of the legs, especially the right, and there was marked tenderness of the muscles of the right calf and in the right popliteal space, and slight tenderness over the same areas in the left leg. From July 19 to 22 he complained also of pain and tenderness in both forearms. July 26, severe coughing attacks throughout night. August 6, pain in side of chest. August 17, two severe chills. August 18, tenderness and palpable cord in right femoral region and in popliteal space and swelling of tissues calf. August 19, suddenly developed labored respiration with cough and blood-streaked expectoration. These symptoms continued until August 22 when he died. No autopsy.

Case 28.—A. M., female, aged twenty-five years. No. 178318. Admitted July 29, 1911. Patient had been ill for four weeks but had not gone to bed. On admission the dilated and tortuous superficial veins on the inner and anterior aspects of both legs and thighs were thrombosed, dark in color, and tender to pressure. On August 7, patient suddenly became restless and dyspneic, complained of pain in the chest, and, later in the day, showed at the base of the right axilla an area of diminished breathing over which were many fine rales. The pulmonary symptoms continued; the signs remained unchanged and three days later the patient died. No autopsy.

Case 29.—B., male, aged twenty-one years. No. 178517. Admitted August 10, 1911, on sixth day of disease. Very mild initial course. After temperature had been normal for nearly five weeks it began (September 27) a step-like ascent, accompanied by general malaise and pains in the back and limbs. October 4, tenderness over right femoral and popliteal veins and pain in calf. October 8, had restless, sleepless night, and complained of pain in chest. No cough. The signs of phlebitis gradually disappeared. The fever lasted a considerable period. There were no further pulmonary symptoms.

PHLEBITIS WITH PULMONARY SYMPTOMS OF DOUBTFUL NATURE

Case 30.—P., male, aged twenty-two years. Admitted November 20, 1897. Pulmonary signs at one base, with rise of temperature after defervescence. One month later frank signs of bilateral femoral phlebitis.

Case 31.—H., female, aged twenty-six years. Admitted December 9, 1897. Pulmonary signs at right base late in disease. Rise of temperature and rapid pulse. Three weeks later phlebitis right femoral vein.

Case 32.—H. W. L., male, aged thirty-five years. No. 5341. Early pulmonary symptoms (severe cough and blood-streaked, frothy sputum). Later extensive phlebitis of both legs and right arm.

Case 33.—C. S., female, aged twenty-three years. No. 8695. Slight early pulmonary symptoms, probably not embolic. Two weeks later phlebitis of left femoral vein.

Case 34.—D. E. D., male, aged twenty-four years. No. 13097. After defervescence sudden cyanosis followed by rise of temperature and pain in region of diaphragm on left side. Five days later phlebitis of right external saphenous vein.

Case 35.—G. G. B., female, aged twenty years. No. 14095. Very severe course; patient delirious much of time. Between July 19 and 26 troublesome cough with slight expectoration. July 26, at 6 A.M., sudden cyanosis and collapse. July 28, "very free expectoration." July 29, "complains of toes being painful." On August 12 temperature after having been normal for five days began to rise. August 14, troublesome cough. August 17, pain in right leg above foot. August 29, severe pain in left leg, with rise of temperature. Later signs of phlebitis in both legs.

Case 36.—A. W., female, aged twenty-eight years. No. 16313. During fifth week troublesome cough with rales, especially at right base. Two chills. Ten days later phlebitis of left femoral and calf veins.

Case 37.—J. T., male, thirty-two years. No. 176408. During defervescence troublesome cough for two days. Five days later signs of left femoral phlebitis with chill and high temperature.

PULMONARY SYMPTOMS SUGGESTIVE OF EMBOLISM WITHOUT EVIDENT PHLEBITIS

Case 38.—M. K., female, aged twenty-four years. No 2045. Admitted March 13, 1899. Average uneventful course. At end of defervescence sudden, severe pain in right side of chest. Three days later severe pain in toes of both feet, lasting several days. No other signs of phlebitis.

Case 39.—J. D., female, aged fifty-three years. No. 2807. Admitted August 31, 1899. Normal and uneventful course until September 24; then at 2 A.M. sudden collapse with rapid breathing, weak pulse, and cold sweat. Gradual improvement. October 1, sudden, severe pain in left side of chest, requiring morphine. Next day, dulness, bronchial breathing, and crepitant rales over lower part of left lung behind. Signs disappeared in five days. October 8, severe pain in right hypochondrium. October 18, severe *pain* in *right* side of chest, lasting several days. Temperature up during each of the pulmonary attacks. No notes indicating phlebitis.

Case 40.—A. P., female, aged thirty-two years. No. 2888. Admitted September 18, 1899. During fourth week chill and on following day dulness, bronchial breathing and many rales over right lower lobe posteriorly. Two more chills on next day. Three days later sudden death. No mention of phlebitis. No autopsy.

Case 41.—S. N., male, aged nineteen years. No. 4567. Admitted October 7, 1900. Severe, protracted course. Temperature reached normal November 9. Rose abruptly November 15, without apparent cause and remained up for several days. December 1, chill with rise of temperature to 106° F.; down next day, December 3, two chills. December 5, sharp pain in right side of chest, cough, and many fine rales at right base and in lower part of right axilla. Pain, cough, and pulmonary signs lasted for 10 days. Temperature high and irregular for some days longer and then fell gradually. No mention of phlebitis.

Case 42.—J. N., male, aged thirty-four years. No. 6355. Admitted October 7, 1901. Ran a moderate course, the temperature reaching normal on October 20, and remaining so until October 23. On this day it rose somewhat. On the next it reached 103° F. and there was pain referred to the upper part of the abdomen. On October 25 the pain was localized in lower part of left axilla and a pleuritic friction rub was present. October 28, chill. October 29, temperature still high, troublesome cough, and signs of a small area of consolidation near spine of left scapula. On the following day most of these signs had disappeared. Temperature reached normal on November 4. No mention of phlebitis.

Case 43.—T. C., male, aged twenty-six years. No. 8233. Admitted September 30, 1902. General condition good; lungs clear. On twentieth day (October 5) pain in left side of chest and friction rub. Two days later signs of fluid. Turbid, serous fluid removed from left chest. More fluid removed on October 10 and 12. October 13, at 5 p.m., patient died, apparently suddenly and unexpectedly. No autopsy. No mention of phlebitis.

Case 44.—E. N., male, aged twenty-six years. No. 8480. Admitted November 20, 1902. Late in the disease sudden pulmonary signs with cough and bloody sputum. Then a "relapse" during which there were several chills and sweats. No notes indicating phlebitis.

Case 45.—K. E., female, aged forty-three years. No. 8872. Admitted January 31, 1903. Developed typhoid while in hospital. On thirtenth day (March 22) cough, expiratory grunt, and small area of dulness above angle of left scapula. Several days later signs of consolidation at *right* base. Some time later, after temperature had reached normal, had a "relapse" with slight rise in leukocytes (10,000) but no note to indicate presence of phlebitis.

Case 46.—R. R., female, aged twenty-six years. No. 9115. Admitted March 14, 1903. Severe but uneventful course. Temperature reached normal April 18. One week later temperatu e rose again without discoverable cause. Leukocytes, 9000. May 4, sudden onset at night of severe pain in left hypochondrium. This pain lasted several days, was made worse by deep breathing or coughing. The fever continued for some days after subsidence of the thoracic symptoms. No other indications of phlebitis.

Case 47.—W. K., male, aged twenty-seven years. No. 9979. Admitted October 3, 1903. Fairly severe course. On eighteenth day (October 5) sudden severe pain in right axilla, followed next day by friction sounds in the same region. These signs lasted for ten days. Gradual defervescence. No notes indicating phlebitis.

Case 48.—E. B. A., female, aged nineteen years. No. 10002. Admitted October 7, 1903. Moderate course. Temperature had been almost normal for several days when on October 18, it rose again and ran a high and irregular course for some weeks. October 20, severe pain in right side of chest and many fine rales in axilla. Next day cough and bloody sputum. Leukocytes, 19,000. October 25, still spitting up blood. Signs of consolidation in right interscapular region. October 26, sudden collapse with pallor, feeble pulse, etc. October 27, severe pain in right upper quadrant of abdomen, with course friction rubs at base of right lung. Cough and bloody sputum. November 9, severe pain in *left* side abdomen, with pleuritic rales in left axilla. Cough with occasional bloody sputum continued some days longer. Eventual recovery. No notes to indicate phlebitis.

Case 49.—C. W., female, aged twenty-four years. No. 10181. Admitted November 27, 1903. Mild course. By December 5, temperature had fallen to about 100° F. Sudden pain in back, difficulty in breathing, and rise of temperature. On the next day the pain had become localized in left side of chest and was intense. Temperature 105° F., respiration 48, pulse 140. Leukocytes, 13,000. December 8, bronchial breathing and voice over upper part of left lower lobe, with dulness, diminished breathing, and fine rales at the base. By December 11, the signs of consolidation had disappeared and the general condition was much improved. Two weeks later patient began to have small, bloody, mucous stools with much pain and tenesmus (thrombosis of hemorrhoidal veins?). No other indications of phlebitis.

Case 50.—J. L., female, aged sixteen years. No. 13337. Admitted December 28, 1905. Fairly severe course. Troublesome cough for several days during fifth week. Later an apparent relapse and during this, signs of pleurisy with effusion at left base. No leg symptoms.

Case 51.—J. R. L., female, aged twenty-eight years. No 13373. Admitted January 4, 1906. Very severe course. Late in the disease signs of consolidation in right lower lobe, with chills and marked leukocytosis. Rapid resolution. No leg symptoms.

Case 52.—L. I., male, aged thirty-eight years. No. 13440. Admitted January 19, 1906. Mild attack. January 25, began to have burning pain starting just below and inside left shoulder and extending down forearm to hand, with inability to flex thumb and index finger. From February 6 to February 13, profuse sweats every night. February 15, sharp pain in right side of chest on breathing, with dry rales on inspiration. The tem-

perature after being normal for a week began to rise on January 31 and remained elevated for three weeks. The pain in the arm lasted for several weeks.

Case 53.—A. M., female, aged twenty-two years. No. 14128. Admitted July 18, 1906. Moderate course. At end of fourth week, with temperature almost normal, pain, and signs of dry pleurisy in left side and rise of temperature. Ten days later (August 10) signs of dry pleurisy at base of *right* lung. August 13, sudden severe pain in left side of chest and left shoulder, with a few crepitant rales in left axilla. No further symptoms. Rapid recovery. No notes indicating phlebitis.

Case 54.—L. G., female, aged twenty-five years. No. 14211. Admitted August 10, 1906. Moderate course and long relapse. Toward the end of this signs of consolidation at base of right lung. Death. No autopsy. No indications of phlebitis.

Case 55.—W. M., male, aged eighteen years. No. 14528. Admitted November 2, 1906. Moderate course. At end of fourth week, with temperature low but unsteady, symptoms of severe plastic pleurisy at base of right lung which lasted for one week. No notes indicating phlebitis.

Case 56.—H. S., male, aged twenty-one years. No. 14625. Admitted November 26, 1906. Fairly severe course. During third and fourth weeks signs and symptoms of plastic pleurisy over lower half of right chest. Temperature reached normal about December 24, and remained so until January 1, when it rose suddenly to 104° F., remained high for several days and gradually fell to normal. No apparent cause for the rise. No notes indicating phlebitis.

Case 57.—S. Q., male, aged twenty-five years. No. 14830. Admitted January 21, 1907. Severe protracted course. At end of fourth week (January 28), with temperature falling, sudden, very severe pain in right chest with rise of temperature and signs of consolidation in right interscapular region. No changes in leukocytes (7000). Temperature reached normal February 2, and remained down until February 7. It then rose rapidly to 104° F., remained high for one week and gradually fell. Later there was another transient rise. Nothing found to explain the temperature. No notes indicating phlebitis.

Case 58.—I. M., male, aged sixteen years. No. 14003. Admitted February 8, 1907. Moderate course, uneventful until February 19, at which time temperature had fallen almost to normal. Then sudden pain in left chest. A few hours later had a chill with moderate rise of temperature. Four days later, when temperature had again become normal, dulness at left base with rales. Two days later sudden transient rise of temperature to 105° F. without apparent cause. Rales persisted for some days. No signs of phlebitis.

Case 59.—E. P., female, aged twenty-six years. No. 15174. Admitted April 3, 1907. Severe course. On twentieth day (April 10) dulness,

bronchial breathing and voice and crepitant rales over both lobes posteriorly. Signs lasted one week. Defervescence by lysis. No material rise in leukocytes. Slow convalescence. No signs of phlebitis.

Case 60.—A. B., male, aged twenty-seven years. No. 15514. Admitted June 18, 1907. Rather mild course. Temperature reached normal on June 28, and remained so until July 2. Then pain in right axilla, cough and "brownish viscid sputum" with rise of temperature. Later signs of fluid. After temperature had reached normal it rose again for a day or two without evident cause. No signs of phlebitis.

Case 61.—C. A. H., male, aged thirty-two years. No. 17579. Admitted October 31, 1908. Moderately severe course. Temperature gradually fell to normal and remained down for four days; then (November 24) began to rise. Pain in left side, and dulness, diminished breathing and friction rubs at base of left lung. Signs of pleurisy and cough lasted two or three weeks. Temperature fell gradually. No notes indicating phlebitis.

Case 62.—M. H., male, aged forty years. No. 18820. Admitted September 23, 1909, on eleventh day of disease. Complained of pains in legs before admission. Slight pretibial edema. Uneventful course until October 20. Temperature running below 101° F. The rise of temperature and pain in lower part of left chest with, later pleuritic friction rubs over same region. No signs of phlebitis.

Case 63.—G. P., male, aged twenty-four years. No. 179816. Admitted November 5, on twenty-second day of illness. Severe course, uneventful until November 15. Then sudden pain in right axilla, followed by friction sounds, cough, and abundant "frothy, blood-streaked sputum." November 20, pain and friction sounds now in *both* axilla. Cough and bloody sputum persisted. Temperature continued high and irregular. Two weeks later signs of small pulmonary abscess in left lower lobe. Operation. Death. No autopsy. No evidence of phlebitis.

THE RELATION OF THE LATE MULTIPLE CHILLS OF TYPHOID TO THROMBOPHLEBITIS

In studying the cases of typhoid with a view to ascertaining the mutual relations between phlebitis and pulmonary and pleural complications it soon became evident that in the cases complicated by phlebitis the occurrence of chills was so frequent as to call for investigation, more especially as in most cases such chills were multiple. These multiple chills of the later weeks of typhoid have never received a satisfactory explanation. After eliminating the rare instances of true malarial chills, and those seen in the course of

pyelitis and other recognizable complications, there remain a considerable number of cases of protracted typhoid in which the latter weeks of the course are punctuated by a succession of abrupt, violent rises of temperature, associated usually with chills and followed often by sweats. For these disturbing symptoms usually no adequate cause can be found, and, although the blood cultures are uniformly negative and the leukocytes frequently show no significant change, these obscure cases are apt to be regarded as instances of post-typhoid sepsis. A further characteristic feature of these cases, in my own experience, is that they all ultimately recover.

Among the total number of cases of typhoid fever reviewed multiple chills occurred in 20 instances. In 16 of these 20 cases (80 per cent.) there were well-marked signs of thrombophlebitis. In every one of the 4 cases in which no signs of phlebitis were observed there were pulmonary symptoms strongly suggestive of pulmonary embolism (see Cases 40, 41, 44, and 51). In 10 of the 16 cases with phlebitis, also, there were symptoms of pulmonary embolism. Sometimes the chills would coincide with the onset of the pulmonary symptoms; occasionally they would synchronize with a fresh exacerbation of the phlebitis, but frequently they occurred without other symptoms and without apparent reason. In 7 cases all the chills occurred before any of the signs of phlebitis were apparent. Four of the cases have already been cited (Cases 2, 9, 24, and 36); the others follow:

Case 64.—C. G., male, aged twenty-six years. No 8488. Admitted November 22, 1902, on sixth day of illness. Moderate course. By November 27 temperature had fallen to 100° to 102° F. This continued until December 3 when temperature began to run higher. Chills occurrred on December 7, 8, 10, 11, and 12. On December 31 patient complained of pain in calf of right leg and three days later there was tenderness over the calf in the popliteal space and over the upper portion of the femoral vein. The temperature which had been about normal for some days began to rise on January 1 and remained elevated for two weeks. Meantime there were symptoms of extensive phlebitis of the right thigh and leg with, ultimately, slight edema. No pulmonary symptoms.

Case 65.—C. K. W., male, aged forty-eight years. No. 12626. Admitted June 21, 1905, on fifteenth day of disease. Fairly severe course. Between July 1 and 4 there were five chills, occurring without known cause, and

during this time the leukocytes ranged between 4000 and 5300. On July 7 the right leg became painful and swollen and there was tenderness over the course of the femoral vein. On July 12 the left leg became similarly involved. No further chills. No pulmonary symptoms.

Case 66.—J. V., male, aged sixteen years. No. 17160. Admitted July 19, 1908, on seventh day of illness. Moderately severe course. On July 22 and 23 severe intestinal hemorrhages. On July 24, 25, and 29 chills without apparent cause. August 2, "lungs clear except for scattered rales." Course uneventful until August 23 when there appeared signs of phlebitis in left groin. These later involved the left leg and were associated with edema. No pulmonary symptoms. In six instances the chills took place both before and during the obvious manifestations of phlebitis. Cases 3, 6, and 13, and

Case 67.—J. H. J., male, aged twenty-four years. No. 2634. Admitted July 26, 1899, on twentieth (?) day of disease. Severe course. Very sick and delirious for a number of days. Between July 31 and August 15 there were six chills. On August 17 symptoms of phlebitis appeared in left leg and a few days later in the right leg. Further chills occurred on August 27 and 29, and September 2 and 6. The phlebitis ran a long, severe course. No notes of any pulmonary complications.

Case 68.—O. H., male, aged thirty-two years. No. 4110. Admitted July 4, 1900, on fourteenth day of disease. Moderate course. July 15 chill with rise of temperature to 105° F. During next three days gradual fall in fever to 100° F., then (July 19) chill and rise to 105° F. After that temperature continued high for some days. July 23, pain and tenderness over upper part of left internal saphenous vein and five days later signs of involvement of femoral on same side. Between July 24 and 31 five further chills. Slow convalescence. No pulmonary symptoms.

Case 69.—R. R., female, aged twenty years No. 12894. Admitted August 29, 1905, on sixth day of disease. Fairly severe course. September 13 (nurse's note) "Complains of pain in feet. Left foot and ankle considerably swollen." From September 13 to October 1 patient had almost daily chills without obvious cause. Blood cultures were sterile, there was no rise in the leukocytes and physical examination of the chest was negative except for scattered sibilant and sonorous sounds. On September 19 a tender, elongated mass could be felt over the upper part of the left femoral vein and there was slight edema of both ankles. The symptoms soon subsided and it was not until October 25, after the patient had been sitting up for a few days, that frank symptoms of milk leg appeared. No pulmonary symptoms.

In 3 cases the chills did not occur until after the phlebitis had declared itself (Cases 21, 23, and 25).

In view of the fact that in 80 per cent. of the cases of typhoid marked by the occurrence of multiple chills of unknown cause there was present also thrombophlebitis, and of the further fact that in all of the few remaining cases, in which no phlebitis was recognized, there occurred symptoms suggestive of pulmonary embolism, it is difficult to escape the conclusion that these obscure "post-typhoid" chills bear some very direct relation to the thrombotic process in the peripheral veins. Just what that relation is, in every case, it may not be easy to say. Such rigors are probably not always due to the same cause. It is not uncommon for a chill to accompany the onset of symptoms of phlebitis of a large vein or to mark the sudden extension of such a phlebitis; but these are usually only single chills, and this explanation fails entirely to account for the very characteristic type of cases we are considering in which chills may have been occurring almost daily for two or three weeks before any symptoms of phlebitis have appeared. A good many of the chills occurred simultaneously with the onset of symptoms of pulmonary embolism, but in these same cases some of the chills would take place *without* such pulmonary symptoms, and the question arises as to whether a rigor may not at times be the only recognizable symptom of the lodgement of a tiny embolus. Gerhardt,[11] in his classical description of the hemorrhagic infarct, says: "The act of embolism can pass almost or quite without symptoms when small fragments of clot enter a sound lung or where marked dyspnea already exists." He also speaks of a chill as a frequent symptom of embolism. Even upon the assumption, however, that some of the chills which appear without accompanying pulmonary symptoms may be due to tiny emboli, the problem does not seem to be altogether solved; for occasionally a case is met with in which, although there are many chills, there are no pulmonary symptoms with any of them. It seems very unlikely that twelve or fifteen attacks of pulmonary embolism should occur without some of them presenting characteristic symptoms or physical signs. For such cases it must be acknowledged that there is, at present, no satisfactory explanation.

The literature contains a good deal of evidence in support of the view that the late multiple chills of typhoid bear some constant

relation to thrombophlebitis; although this relation appears never to have been fully recognized. The reason for this seems to lie in the fact that the chills often begin two or three weeks before the usual symptoms of phlebitis appear. Heringham[12] recorded 6 cases of multiple chills. In 4 of these the existence of thrombosis was recognized and in one other the symptoms as described strongly suggest thrombosis. Saw[13] reports two typical cases of "septic" chills, in both of which there was venous thrombosis, and in one also a late and severe pulmonary embolism.

Leclerc[14] and Howland[15] each report a case of multiple chills accompanied by thrombophlebitis.

Thayer[2] found that in 28 per cent. of his cases of venous thrombosis complicating typhoid there were chills, and adds: "In the last two years I have seen in consultation three further cases in which otherwise unaccountable chills during convalescence from typhoid fever were followed by a complicating thrombosis."

THE RELATION OF THE SYMPTOM OF "TENDER TOES" TO THROMBOPHLEBITIS

The study of the cases of phlebitis complicating typhoid fever brought out the further fact of the frequent association of such cases with the interesting symptom known as "tender toes." This condition of painful and exquisitely tender toes is, as is well known, an occasional complication of typhoid and always appears late in the disease or during convalescence. It is commonly regarded as a neuritis of the plantar nerves, although in many instances the transient character of the symptoms, as well as the lack of trophic changes, suggests that the process can hardly be an actual neuritis. Among the 1540 cases of typhoid reviewed this complication is recorded 22 times. In 12 of these cases (55 per cent.) there was also the complication of phlebitis of the legs. In 7 of the cases the tenderness of the toes was complained of before the appearance of the symptoms of phlebitis; in 5 cases the signs of phlebitis appeared first.

Nine of these 12 instances of the association of tender toes with

manifest phlebitis have already been cited (Cases 4, 5, 7, 12, 22, 24, 25, 35, and 69).

The remaining three are given below:

Case 70.—F. B., male, aged twenty-one years. No. 1278. Admitted October 4, 1898, on tenth day of disease. Average course. Temperature reached normal October 28. On October 20 first complained of "tenderness of toes." Allowed up in chair on November 2. Next day pain in left leg and on following day pain, tenderness, and swelling in left calf. No temperature with the phlebitis.

Case 71.—F. P. S., male, aged thirty-seven years. No. 11735. Admitted December 8, 1904, on fifteenth day of disease. Moderate course. Temperature fell rapidly to 100° on December 24, then rose slightly for five days, then fell to normal. From December 27 to 31 patient has pain and tenderness in left foot and toes. January 2 signs of phlebitis in left thigh and calf.

Case 72.—P. E. C., female, aged nineteen years. No. 17290. Admitted August 19, 1908, on tenth day of disease. Temperature reached normal by August 27. On August 30 the temperature rose slightly and remained somewhat elevated for several days. On August 31 there was severe pain in the left groin and upper part of thigh with all the usual symptoms of femoral and popliteal phlebitis. For the period of a week after the onset of these symptoms there was pain and tenderness in the sole of the left foot, toes and heel.

In addition to the above-mentioned cases of tender toes there were several cases of phlebitis in which pain and tenderness of the heel were the first indications of phlebitis in that leg.

Tender Toes without Signs of Phlebitis. An analysis of the 10 cases of tender toes in which there was none of the usual evidences of phlebitis shows that in 7 of these there was at the time of the appearance of the painful and tender toes an irregular and unaccountable post-typhoid febrile movement. In one of the three remaining cases there were the symptoms of pulmonary embolism.

Case 73.—W. H. S., male, aged twenty-four years. No. 1043. Admitted September 5, 1898. Severe course. Temperature reached normal on September 20. On September 22 began to complain of severe pain and tenderness of feet and toes which lasted for some days. September 24, temperature rose to 102° F. and fell to normal next day. Later patient ran a high and irregular temperature for twelve days, with no apparent cause.

Case 74.—M. K., female, aged twenty-four years. No. 2045. Admitted March 13, 1899. Average course. Temperature reached normal March 26. On March 24 sudden pain in right side of chest. March 27 and for several days thereafter pain and tenderness of toes of both feet. No temperature. No notes indicating phlebitis.

Case 75.—T. K. B., male, aged thirty-seven years. No. 6278. Admitted September 26, 1901. Protracted but not severe course. Temperature reached normal by November 4. On October 29 there was noted "pain and tenderness along the course of both internal plantar nerves, especially the left." No evidence of phlebitis.

Case 76.—B. E., male, aged twenty-eight years. No. 6307. Admitted October 1, 1901. Protracted course. Two early and small hemorrhages. On October 14 first complained of tenderness of feet, especially on pressure. Between this date and November 17 there are several references to the continued tenderness and pain in the feet. On the nights of November 4 and 5 there were severe paroxysms of coughing. On November 26 there were local applications to the legs apparently because of pain. After October 16 the temperature ran a high and irregular course. On October 23 there was a sudden rise to 106.8° F. It reached normal first on November 11 but did not remain constantly so until November 30.

Case 77.—B. B., female, aged forty-four years. No. 6374. Admitted October 11, 1901. Short, mild course. On admission "slight edema of the extremities." Between October 21 and 24 severe pain and tenderness in toes and soles of both feet. No further symptoms.

Case 78.—M. S., male, aged twenty-four years. No. 7800. Admitted July 14, 1902. Moderate course. Defervescence complete by August 4. On August 11 began to have pain and tenderness in toes of right foot which lasted eight or nine days. With this slight rise of temperature for three days. No other symptoms.

Case 79.—B. S., female, aged twenty-two years. No. 9828. Admitted August 22, 1903. Long, severe course. Severe bronchitis during the early weeks. On September 6, first complained of tenderness of toes. September 8, slight edema of feet and tenderness low in the right iliac fossa but no tenderness over either femoral vein. The pain and tenderness in the toes was present almost constantly for the next two months. The temperature which had gradually fallen to about 100° F. began on September 17 to rise again and then ran a high and irregular course for the next six weeks without any local symptoms.

Case 80.—C. G. F., male, aged thirty years. No. 12904. Admitted August 31, 1905. Course of average severity. During convalescence and with normal temperature complained for several days of tenderness of toes. No rise of temperature. No other symptoms.

Case 81.—G., male, aged fourteen years. No. 9668. Admitted July 10, 1903. Fairly severe course. On twenty-third day first complained of

soreness of toes and soles of feet. The tenderness and pain was very troublesome for four days and then disappeared. Later a short "relapse." No other signs of phlebitis.

Case 82.—C. E., female, aged twenty years. No. 10858. Admitted May 6, 1904. Mild, initial attack, followed by severe, prolonged relapse. During this complained of tenderness of toes and feet. Following this, prolonged, irregular, but not high temperature. No notes indicating phlebitis.

From the foregoing facts one is, of course, not justified in accepting as proved the causal relation between phlebitis and the symptom of tender toes; and yet the association of the two conditions is much too frequent and striking to warrant the assumption that this association is merely a fortuitous one. It seems unlikely that thrombosis and inflammation of the small veins of the foot should of themselves produce the symptoms under discussion. It seems to me more probable that there is first a thrombosis of one or more of the veins in the region of the heel and that the subsequent periphlebitic exudate may in some cases be sufficient to irritate, or actually to cause an inflammation of, the adjacent plantar nerves. A moment's reference to any good anatomical plate of the deeper structures of the sole of the foot will show how very close is the approximation of the two plantar arteries, with their venæ comites, to the corresponding internal and external plantar nerves. Especially at the heel, where the posterior tibial artery, with its veins, curves over the astragalus to reach the sole of the foot, the vessels and nerves are in very close contact. There also it seems likely that the angular bend in the veins may predispose to the development of thrombosis and phlebitis. This hypothesis receives clinical support from the fact that pain and tenderness of the heel are not uncommon symptoms in thrombophlebitis.

It seems to me quite possible that some or most of the cases of *localized* neuritis which complicate typhoid fever may be found to be due to periphlebitic inflammation from some adjacent, thrombosed vein, for in all the extremities the deep vessels and nerves are generally found in close proximity to each other. In Case 9 of this series, in which there was phlebitis of the left femoral and

popliteal veins, there was evidently an associated neuritis, as shown by the weakness of the anterior tibial group of muscles in the affected leg.

THE TEMPERATURE IN THROMBOPHLEBITIS

A febrile movement of some degree was present in all but about 10 per cent. of the cases of thrombophlebitis. In a majority of the cases the temperature rose with the appearance of the signs of thrombosis of a large vein. Not infrequently, however, the febrile movement began several days or even longer before any of the usual symptoms of thrombosis had appeared. Every possible variation, as regards time of appearance, duration, severity, type, etc., was encountered in studying the behavior of the temperature in the cases of typhoid complicated by phlebitis. In a number of the cases there was fever for some days preceding the appearance of signs of phlebitis, but no fever afterward. In others the temperature rose only after the phlebitis had been manifest for several days. The vagaries of the temperature curve are well shown in the cases cited in the section relating to multiple chills. In a good many of the cases after the period of typhoid defervescence had become nearly or quite complete the temperature would rise again and then run a long and irregular course, in the midst of which at some time appeared the signs of venous thrombosis. Sometimes this post-typhoid fever was accompanied by chills; sometimes there were sudden, short rises of temperature without an accompanying chill and without apparent cause.

Such late and prolonged periods of fever are often regarded as relapses or recrudescences of the typhoid process, but it is not difficult I think to distinguish between a true relapse and the type of fever under consideration. In going over the temperature charts of a large number of cases of typhoid I have been led to the conviction that in all uncomplicated cases of typhoid the fever curve is strikingly uniform and constant in its general type, although varying much in its duration, its severity, and to some extent in the length of its periods of ascent and defervescence. Any radical departure from this familiar type usually indicates the

existence of some complication, even though the complication may not always be readily discoverable. The same statements, I believe, apply to the true and uncomplicated relapse. There is the more or less gradual ascent, the period of continuous elevation, and the period of defervescence; and the chart of such a true relapse bears little or no resemblance to the various types of post-typhoid temperature described above. Sudden violent remissions or exacerbations; greatly prolonged, slight, febrile movements; the occurrence of chills, are all indications that the fever is not that of a true relapse but is due to some complication or sequel. In such cases, when the various other possible complications have been excluded, there will usually be found sooner or later some symptoms to indicate the existence of a thrombophlebitis. Many of the sudden and transient rises of temperature seen during convalescence from typhoid and usually ascribed to errors in diet are unquestionably due to this cause. The fact that a febrile movement may have existed for two or three weeks before any signs of phlebitis of a large vein have appeared cannot be held to invalidate this view as to the association of the two conditions, for there is an abundance of evidence to show that the phlebitic process may remain latent, or nearly so, for a period of several weeks.

No entirely satisfactory explanation for the occurrence of fever in the course of a latent phlebitis can be given at present. Bock[16] has recently shown by experiments upon animals that the intravenous injection of some indifferent and sterile substance, such as paraffine, in a finely divided state, is regularly followed by some rise in temperature. It is possible that some of the elevations of temperature seen in the early stages of phlebitis may be caused by the separation of tiny fragments of the thrombotic material before the vein has become occluded. Whatever may be the true explanation, the fact is beyond question.

Vaquez,[6] speaking of the behavior of the temperature in phlebitis, says: "We believe, for our part, that very frequently a notable elevation of temperature precedes the appearance of phlegmasia alba dolens, but that this elevation of temperature should be sought for not on the day, or the second day, before the first apparent manifestation, but often eight, ten, or twelve days before."

The Leukocytes. In most of the cases there was some rise in the number of leukocytes, and some increase in the proportion of the polynuclear cells, at the time of the appearance of frank signs of phlebitis of a large vein. The increased leukocyte count varied from 10,000 to 26,000. In some cases there was no appreciable rise in the leukocytes at any time, and in many cases a leukopenia persisted for some time after the appearance of the first indications of involvement of the veins. The absence of a leukocytosis cannot, therefore, be used as evidence against the existence of venous thrombosis. The increase in the leukocytes seems to depend chiefly upon the presence of a well-marked periphlebitis.

In the present article it has been my aim not to cover every possible symptom and complication of thrombophlebitis as it is seen in typhoid fever, but to call attention to several interesting groups of symptoms not usually regarded as having any direct relation to venous thrombosis, and no attempt to demonstrate that such a direct relation does actually exist. But this study of the late complications of typhoid in relation to venous thrombosis brought to light a number of interesting and suggestive facts whose significance is not yet clear, and which have not been discussed here; but which, nevertheless, are worthy of study and elucidation. Indeed, it is hardly too much to say that the whole symptomatology of the latter weeks of typhoid requires to be studied anew from the standpoint of the possible relation of the various symptoms to thrombophlebitis. For example, the relation of thrombosis of the veins of the mesentery and of the intestinal wall to the abdominal symptoms of typhoid is altogether unknown. The fact that in the routine postmortem examination of typhoid cases such thromboses are rarely if ever discovered is by no means proof that they do not occur. Thrombosis of the smaller veins could readily pass unrecognized unless special attention were directed to their examination. In reading the protocols of the cases complicated by phlebitis I have been struck by the frequency with which various obscure abdominal and intestinal symptoms occur. It is possible that some of the attacks of sudden abdominal pain, tenderness, and distention which often closely simulate the symptoms of perforation; that some of the dysenteric symptoms; that some

of the repeated, small, intestinal hemorrhages, may have their origin in thrombosis of the small mesenteric veins.

Two other late complications of typhoid may be mentioned as being worthy of investigation as to their possible connection with thrombophlebitis. One is periostitis, which appeared in a number of the cases during the course of a phlebitis. The other is the rare complication of inflammation of the breasts. In a woman with thrombosis of the veins of the legs there appeared first in one breast and then in the other a phlebitis of one of the veins near the periphery, which was followed by an extensive periphlebitis, so that the condition might easily have been mistaken for a primary mastitis. One cannot but wonder if in all the instances of so-called mastitis complicating typhoid the process may not have begun as a thrombosis of the mammary veins.

Summary. The opinions set forth in the preceding pages may be briefly summarized as follows:

1. Thrombophlebitis is a much more frequent complication of typhoid fever than is generally supposed, and probably occurs in from ten to fifteen per cent. of all cases. Its development is gradual; its course frequently latent for many days, and its classical symptoms usually appear only at a late stage of the condition. The thrombotic process is apt to be much more extensive and more widely disseminated than the pronounced local symptoms would suggest.

2. Most of the pulmonary and pleural complications which appear late in the course of typhoid are due to embolism of branches of the pulmonary artery, and this in turn is due to a complicating venous thrombosis. Such emboli are usually small and their symptoms are frequently mild and transient. The emboli seem to arise chiefly from the freshly formed, friable thrombi in veins which have not yet become occluded; and their symptoms, in a majority of the cases, appear before the usual symptoms of phlebitis are observed.

3. The obscure, late, recurring chills of typhoid are regularly associated with venous thrombosis, although the latter is frequently latent at the time of the appearance of the chills. Some of the chills are certainly related to the lodgement of pulmonary emboli.

4. The symptom of "tender toes" can be shown to be associated with thrombophlebitis in a majority of the cases. The suggestion is made that this symptom may be due to irritation or inflammation of the plantar nerves, which is set up by periphlebitic inflammation from adjacent thrombosed veins in the sole of the foot or about the heel.

5. Many of the unaccountable rises of temperature seen during convalescence from typhoid and most of the protracted and irregular types of "post-typhoid" fever are due to thrombophlebitis.

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DISCUSSION

Dr. F. P. Kinnicutt: Dr. Conner's views on the pathology of certain clinical phenomena of late typhoid are of great interest. Since my attention was called to them by Dr. Conner, a study of several cases presenting clinical phenomena similar to those described has convinced me of the probable correctness of the explanation offered by the author of the paper. In the matter of tender toes, the consensus of opinion is that it is due to

a neuritis, but the suggestion that the neuritis was a secondary process seems very reasonable. The sequence would be a thrombophlebitis, a periphlebitis, and extension of the inflammation or an irritation of the nerve branches immediately contiguous to the affected vein.

Dr. E. Libman: This paper of Dr. Conner seems to me an unusually valuable one. For some years back I have suspected that the sharp temperature rises and the chills seen in cases of typhoid fever, particularly toward the latter part of their course, might be due to thromboses. In such case blood cultures are often negative.

I should like to ask Dr. Conner whether he has been able to determine by blood examinations in cases of thromboses in general whether they are purulent or not. I found in some cases of non-suppurative thrombosis that while the total leukocyte count and the polymorphonuclear count were as high at the onset as in purulent cases, the polymorphonuclear count did not remain as high later in the course of the case.

Dr. W. S. Thayer: I have long been impressed by the frequency with which evidences of thrombosis follow chills or sudden elevations of temperature in the course of typhoid fever, and Dr. Conner's figures are exceedingly interesting.

Although pulmonary manifestations, in these cases, may often be due to embolism, yet one should remember that autothonous thrombosis may occur in the branches of the pulmonary arteries. I remember several instances where such thromboses were found at necropsy.

The question as to the cause of these thromboses is an exceedingly interesting one. The tendency has been to regard the primary element as a phlebitis, but yet it must be said that we have not a definite proof of this in all, or, indeed, in many cases. In connection with the recent awakening of interest in the causes of coagulation of the blood, and in the study of the various blood ferments, it may perhaps be hoped that further information in regard to the cause of some of these typhoid thromboses may be obtained.

Dr. Alexander McPhedran: I have for a good while observed these cases with a good deal of interest. In many of them the phlebitis affects the superficial veins. Two years ago I saw a young woman who had thrombosis of the veins of the leg, chiefly of the left, and a few of the right, also of the left side of the abdomen, the superficial veins being all affected, as were also some of the veins of the arm. Another case is in the hospital at present. The man was very ill; lately he had swelling confined to the middle of the left lower extremity. There was no tenderness of the femoral vein, or localized tenderness elsewhere. Why

should these cases be called thrombophlebitis? Should not phlebitis suffice?

Dr. William H. Welch: Of course the nomenclature of thrombophlebitis is quite an interesting chapter, too long to go into. Phlebitis was formerly the name, and Victor contended that inflammation of vein wall and phlebitis must be an inflammation of the vein wall. The old idea was substituted for Vierodt's thrombosis, which I think reconciles old and present views. The name thrombophlebitis has that history. The occurrence of small plugs in the vessels without bad results, which we have always supposed that the clinician could not recognize, is a familiar fact in pathological anatomy in typhoid fever. Plugs in the musculocutaneous veins which merely anastomose, but they are known to pathologists, and Flexner made something of a study of them in my laboratory in reference to the interpretation of the plugs in the smaller vessels, and he came to the conclusion that many of them could be interpreted as collective thrombi. Dr. Conner gives the pathologist some new work to do. The contention that is based to a very considerable extent to definite small emboli in typhoid fever in branches of the pulmonary artery, it is a well-known fact that pulmonary embolism leaves no infarction at all, and we have to find some other causes. It takes careful systematic study to determine the proportion of cases in which plugs in branches of the pulmonary artery give rise to venous thrombi in typhoid fever which would leave record behind. Perfectly bland emboli there are often found upon careful search without any infarct and without any pneumonia. I think it is an extremely interesting contribution. The difficulty for the pathologists is that they cannot make these dissections of the extremity at the autopsy.

Dr. B. Sachs: May I be allowed to call attention to the frequency of these conditions of thrombophlebitis in the lower extremities and the circumstances under which they are recognized. It is interesting to hear of the frequency with which they occur in typhoid fever. In the senile and presenile period these conditions are extremely frequent, although very generally overlooked. I am very certain that many of the conditions not only of moderate paresis, but particularly of leg pains occurring in older persons are distinctly due to the condition of thrombophlebitis. The anatomical substratum of these conditions is also similar to that found in erythromelalgia. Some years ago it was supposed that the neuritis was the primary condition, but now it is established that thrombophlebitis is the primary condition and the neuritis is entirely secondary. The point I should like to ask is this: Has Dr. Conner any idea as to the length of time the tender toes persist? In the condition I have been acquainted

with in which the anatomical substratum has been established, the tender toes would not persist for any considerable period of time without trophic disturbance of the skin.

Dr. S. Solis Cohen: Did Dr. Conner observe in any of the cases in which he has made clinical studies an excess of blood platelets? Many years ago in studying the blood in typhoid fever I found in some cases an excessive tendency toward fibrillation of the blood upon the slide; and in these cases the platelets were apparently numerous. Exact modern methods of estimation were unknown, and hence unused. I have seen many cases which clinically seemed to be pulmonary infarct, without pleurisy or pneumonia in the true sense of the term, and in which no evidence of extrapulmonary thrombus or phlebitis could be found; but since hearing this admirable paper I shall make more careful search. I can confirm Dr. Conner's observation of the rise of temperature a day or two before phlebitis is demonstrable—also of pain as a premonitory signal. In one case the pain was referred to the right groin and caused suspicion of appendicitis or perforation, but in a few days the "milk-leg" was evident.

Dr. Conner: I am glad to have Dr. Sachs bring out the point that thrombophlebitis, in conditions other than typhoid fever, is of common occurrence. That is unquestionably the case. It is to be found complicating all sorts of illnesses. Sometimes it is seen in persons otherwise apparently well. In their postoperative cases the surgeons are meeting this condition all the time, and frequently they fail to recognize it, or fail to recognize the relationship of the pulmonary symptoms to the phlebitis, which may not manifest itself until some days later. Dr. Libman's question concerning the behavior of the leukocytes I cannot answer very satisfactorily. We found the leukocytes to vary in all sorts of ways. Sometimes there was no material change either in the number or the relative proportion of the leukocytes. In other cases there was a very considerable leukocytosis. The particular point Dr. Libman makes of a high leukocyte count without a correspondingly high nucleosis I have not observed. Dr. Thayer's suggestion that in some cases the pulmonary symptoms may be due to a primary thrombosis of the pulmonary artery rather than to embolism from a venous thrombosis deserves consideration. It is possible that some of the cases of apparent embolism without evidences of venous thrombosis may have been of that nature. The conditions of the circulation in the pulmonary artery, however, are those of the systemic arteries rather than of the veins, and it seems to me probable that the pulmonary artery shares with the other arteries their relative immunity from thrombosis. In reply to Dr. McPhedran's question, I feel quite sure that in these cases the pulmonary symptoms are the effect and not the cause of

the phlebitis. Even when these symptoms appear some days before those of phlebitis they can usually be distinguished from those of a primary pneumonia.

The question as to the true nature of thrombophlebitis is still unsettled. Aschoff, the last to study and write upon this subject, is inclined to believe that the process is primarily one of thrombosis, and that the phlebitis and periphlebitis are usually secondary. He points out a certain analogy between the formation of bars by the deposition of silt in a river and the formation of a thrombus by the deposit of blood platelets, especially at points where the blood stream is retarded and disturbed. It is well known that thrombosis is especially prone to develop at certain points in the venous system. The femoral vein just below Poupart's ligament is one of these. The deep veins of the calf are another, and there is reason, I think, for believing that a third point of predilection is where the posterior tibial vein turns sharply over the heel. In most cases of tender toes that I have seen the symptoms have not lasted very long. Sometimes they are present only for a day or two. Occasionally they have been very persistent and have lasted several weeks. In such cases there must be, it seems to me, an actual neuritis, but I have never observed distinct trophic changes. Thus far we have made no studies of the blood platelets, but that subject seems to have an important bearing on the question of thrombosis, and we are at present taking up the matter in connection with a further study of thrombophlebitis.

THE RETENTION OF FOREIGN PROTEIN BY THE KIDNEY: A STUDY IN ANAPHYLAXIS[1]

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This investigation was undertaken for the purpose of obtaining exact information in regard to two points of prime importance in connection with the physiology and the pathology of the kidney: (1) Does a foreign protein tend to accumulate in the kidney, and (2) if so, is this tendency greater in the presence of a nephritis? The first problem is of importance mainly in connection with the etiology of nephritis; the second, in connection with the prognosis, treatment, and dietetics of nephritis.

It is obvious that the acute nephritides, associated with acute infectious diseases (scarlet fever, diphtheria, etc.), are due either to the poison elaborated by the causal microörganism or to the products of tissue catabolism. Bacterial and protozoan poisons as well as the products of tissue degradation are soluble poisons acting on the kidney cells, either in a specific selective way or through irritation as the result of long-continued contact during a process of gradual elimination. The latter has quite generally been assumed to be the correct explanation, but this assumption has no actual experimental or other data as a basis. One assumes that because the glomerulus is the usual seat of the renal lesion of scarlet fever that the glomerulus is affected as the result of the elimination of the toxins of scarlet fever by this channel. So, also,

[1] Aided by a grant from the Rockefeller Institute for Medical Research.

with cholera and eclampsia, the epithelial lesion is supposed to be due to the elimination of the toxins of these diseases through the cells of the tubules. Likewise in the experimental nephritides, the glomerular lesion due to arsenic and the tubular lesions due to potassium chromate are similarly explained. On the other hand, it is possible that these various poisons may have a specific selective affinity for certain constituents of the various cells of the kidney, and may be "fixed," as it were, in these cells, remaining within such cells for an appreciable length of time, a period greater than that corresponding to the period of mere elimination.

The solution of this problem depends therefore on some method capable of demonstrating that a foreign protein introduced into the blood stream is (1) equally distributed in the blood and organs, or (2) that it is present in greater amount in the kidney than in the blood, or (3) that it may be demonstrated in the kidney after it has disappeared from the circulating blood. Such a method is that dependent on the phenomenon of anaphylaxis, and the suggestion that these problems might be solved by this method, I owe to the papers of Vaughan and his associates,[1] on the parenteral introduction of protein, and to the statement of these investigators that a foreign protein (egg-white) may be detected in the kidney of the rabbit after it has disappeared from the circulating blood.

Previously, Wells had used the anaphylaxis reaction in the study of alimentary albuminuria, and more recently Van Alstyne and Grant have used it to demonstrate the absorption of albumin from the intestine without digestion. Wells found that guinea-pigs cannot be sensitized to egg albumen with the urine of individuals receiving a diet of raw eggs, even when such individuals have an alimentary albuminuria, and concluded that ingested egg albumen does not pass through the body unchanged, and that the albuminuria under such circumstances is due to the elimination of serum proteins and not the ingested foreign protein.

The use of the anaphylaxis reaction to detect foreign protein in the circulating blood or in the organs has been attempted as

[1] V. C. Vaughan, J. G. Cumming, and C. B. McGlumpy. The Parenteral Introduction of Proteins, Zeitschr. f. Immunitätsf. u. exper. Therap., 1911, ix, 16; V. C. Vaughan, J. G. Cumming, and J. H. Wright, Protein Fever, ibid., 1911, ix, 458.

far as I am aware only by Vaughan and his associates and by Van Alstyne and Grant.[1] The latter injected into a vein of a dog 20 c.c. of a mixture of egg albumen and salt solution in equal parts and drew blood after one-quarter of an hour, four, forty-eight, and seventy-two hours. The serum of each of the various samples and the urine for the first period of twenty-four hours were used to sensitize guinea-pigs. An intoxicating injection of egg albumen, at a later period, caused in each animal the characteristic symptoms of anaphylaxis; these being least marked in the animal sensitized with the serum drawn after seventy-two hours, only moderately severe in the animal receiving the forty-eight-hour serum, but severe in all others, including the animal receiving urine. In a second series of experiments Thiry-Vella fistulas were made at various levels of the intestinal canal, egg albumen placed in these and blood drawn at periods varying from one to three hours. The blood serum thus obtained injected into guinea-pigs sensitized these animals to egg albumen. Similar results were obtained with the urine of the first twenty-four hours.

The experiments of Vaughan and his associates may be divided into two groups. In the earlier experiments they used for the sensitization of guinea-pigs the blood of rabbits obtained a few hours after the feeding or injection of egg albumen. In one experiment they found that one and a half hours after intravenous injection of egg albumen (50 c.c. of 1 to 1 solution) the blood failed to sensitize guinea-pigs; in a second, failure was noted after two hours; and in a third, after two and a half hours. In a fourth experiment blood drawn one hour after injection of egg albumen sensitized, while that drawn after, two, three, and five hours failed to sensitize; on the other hand, extracts of brain, kidney, spleen, and liver, made six hours after the injection of egg-white, all possessed sensitizing power, which was most marked in the extracts of the kidney and liver. In a fifth experiment, after the egg-white had disappeared from the circulating blood, the animal was transfused with one liter of salt solution, and samples of fluid were taken from

[1] E. V. N. Van Alstyne and P. A. Grant, The Absorption of Albumin without Digestion, Jour. Med. Research, 1911, xxv, 399.

the heart in amounts of 2 c.c. These had the power to sensitize, as did also extracts of liver, spleen, and muscle; extracts of brain and kidney failed to sensitize.

In a later communication it was shown that extracts of skin, kidney, brain, liver, spleen, intestine, and stomach from rabbits killed twenty-four and forty-eight hours after intravenous injection of egg albumen are capable of sensitizing guinea-pigs, but that similar extracts from animals killed after seventy-two hours do not have this power. The symptoms of anaphylaxis are, the writers note, most marked in pigs receiving extracts of kidney and spleen.

It was this difference between the results at forty-eight and seventy-two hours and the marked reaction in pigs receiving extracts of the kidney that suggested the use of the method of sensitization for the purpose of the present investigation.

Methods. The usual procedure has been to inject intravenously a group of three, four, or five rabbits with a foreign protein, chloroform the animals at intervals of twenty-four hours and inject their blood or the extracts of their organs into the peritoneal cavity of guinea-pigs. After two or three weeks these guinea-pigs received either intravenously or intra-abdominally an injection of the same kind of protein originally injected into the rabbits.

Egg albumen and horse serum have been the substances used in most of the experiments. The egg-white has been diluted with three parts of physiological salt solution, except in some of the earlier experiments in which a dilution of equal parts was tried; as, however, the latter frequently caused sudden death, it was abandoned for a dilution of one part to three. With this dilution no immediate ill effects have been seen, though very rarely an animal has died on the second or third day. All injections have been made into the ear vein; the egg albumen being given in amounts of 40 c.c. of the dilution (10 c.c. of egg-white) and horse serum undiluted in amounts of 10 c.c. All animals have been killed by chloroform except when it was necessary to obtain blood or to wash the organs with salt solution; under the latter circumstances, ether anesthesia has always been used. Organ extracts have been made by grinding the organ in a mortar with sand,

adding 20 c.c. of salt solution, and allowing the mixture to stand at 33° to 35° C. for eighteen to twenty-four hours and then removing the fluid by centrifugation. The extract thus obtained was injected in amounts of 5 to 8 c.c. into guinea-pigs, and defibrinated blood in amounts of 5 c.c. All injections for sensitization have been intra-abdominal.

The intoxicating dose was given in the early work both intra-abdominally and intravenously; in the later work injections were given into the jugular vein only. The amount of egg-white used for intra-abdominal injection was 5 c.c. of a 50 per cent. (1 to 1) dilution and for intravenous injection 4 c.c. of a 25 per cent. (1 to 3) dilution; horse serum was given by these two methods in doses respectively of 5 c.c. and 1 to 2 c.c.

The varying degrees of sensitization, as presented in the following tables, are indicated by the signs which follow:

++++ Acute fulminant anaphylaxis with death and typically insufflated lungs at autopsy.

+++ Marked symptoms—severe respiratory distress, "bucking," convulsions, and prostration, but with eventual recovery.

++ Moderate attack—spasmodic cough, respiratory distress, "bucking," tendency to lie prone.

\+ "Scratching," cough, slight "bucking," slight respiratory distress.

0 No effect.

The following table confirms Vaughan's single observation as to the presence of egg albumen in the kidney twenty-four and forty-eight hours after injection and its absence (or failure to sensitize) after seventy-two hours, and shows the results of control experiments.

Series I. Egg-white.

Rabbits were killed one, two, three, and four days after intravenous injection of 10 c.c. egg-white diluted with salt solution. Pigs received intra-abdominally extracts of kidneys of each rabbit, and after three weeks had elapsed an intoxicating dose of 5 c.c. of equal parts egg-white and salt solution intra-abdominally or 4 c.c. of 1 to 3 dilution intravenously.

	Extract.	Method of injection.	Result
Pig 1	24 hours	Intraperitoneal	+++
Pig 2	24 hours	Vein	++++
Pig 3	48 hours	Intraperitoneal	+
Pig 4	48 hours	Vein	++
Pig 5	72 hours	Intraperitoneal	0
Pig 6	72 hours	Vein	0
Pig 7	96 hours	Intraperitoneal	0
Pig 8	96 hours	Vein	0
Control 1*	.....	Intraperitoneal	0
Control 1*	.....	Vein	0
Control 2*	.....	Intraperitoneal	0
Control 2*	.....	Vein	0
Control 3*	.....	Vein	++++

* Control 1. Normal pigs.

* Control 2. Pigs which had received, twenty-eight days before, extracts of kidney of normal rabbits.

* Control 3. Pig which had received, three weeks before, an extract prepared from normal rabbit's kidney and 1 c.c. of egg-white.

Series II presents the same type of experiment with the use of horse serum instead of egg-white. Here the kidney extract of the third day still retained power to sensitize.

Series II. *Horse Serum.*

Rabbits were killed one, two, three, and four days after receiving 10 c.c. normal horse serum in the ear vein. Extracts of the kidneys of each animal were injected intra-abdominally into guinea-pigs, and after three weeks each pig received 2 c.c. of same horse serum intravenously or 5 c.c. intraperitoneally.

	Extract.	Method of Injection.	Result.
Pig 1	24 hours	Intraperitoneal	+++
Pig 2	24 hours	Vein	++++
Pig 3	48 hours	Intraperitoneal	++
Pig 4	48 hours	Vein	+++
Pig 5	72 hours	Intraperitoneal	++
Pig 6	72 hours	Vein	++++
Pig 7	96 hours	Vein	0
Control 1*	.....	Vein	0
Control 2*	.....	Vein	0
Control 3*	.....	Vein	++++

* Control 1. Normal pig.

* Control 2. Pig which had received, three weeks before, extract of kidney of normal rabbit.

* Control 3. Pig which had received, three weeks before, extract prepared from normal rabbit's kidney and 1 c.c. of horse serum.

At this point it seemed desirable to determine if bacterial proteins were retained by the kidney in a form capable of sensitizing guinea-pigs. The work of others on sensitization to tuberculin and to pneumococcus protein offered some hope of successful

results, and moreover the use of bacterial proteins, factors in the production of nephritis, would, it was obvious, allow more definite conclusions concerning their possible retention in man than would work with egg albumen and horse serum.

Rabbits were therefore given intravenously, tuberculin in the form of "O. T. bovine,"[1] a tuberculin[2] prepared without heating, mallein,[1] mallease,[2] and pneumococcus protein.[3] A vegetable protein, gliadin,[4] was also used.

Extracts of the kidneys of rabbits receiving respectively 25 c.c. of a 2 per cent. solution of gliadin in 0.1 per cent. sodium hydrate, the protein of 6,000,000,000 pneumococci, 10 c.c. tuberculin, and 5 c.c. each of mallein and mallease, all failed to sensitize pigs to the respective proteins.

The disappointing results of these experiments necessitated a return to the use of egg albumen and horse serum as the most satisfactory agents to be used in settling the fundamental points of the investigation. One of these, and the most important, was that of determining the distribution of the egg-white in the body of the injected rabbit. Does a foreign protein tend to accumulate to a greater extent in the kidney than in other organs, or is it present in the kidney in the same concentration as in other organs; in other words, is the content of foreign protein of an organ merely dependent upon the distribution of egg albumen in the circulating blood of that organ? This point was determined by the experiments summarized in Series III and IV, representing the injection of egg albumen and horse serum respectively.

Series III. *Comparison of Sensitizing Power of Blood, Liver, and Kidney after Intravenous Injection of Egg-white.*

Rabbits received 10 c.c. of egg-white diluted with 30 c.c. of salt solution and were killed after twenty-four, forty-eight, and seventy-two hours. Blood and extracts of liver and kidneys were injected into guinea-pigs. After three weeks each pig received intravenously 4 c.c. of 1 to 3 egg-white dilution or 5 c.c. of 1 to 1 dilution intra-abdominally.

[1] Products of Pennsylvania Live Stock Sanitary Board, procured through Dr. John Reichel.

[2] Procured from Dr. John Reichel, of H. K. Mulford Company.

[3] Prepared by Dr. J. A. Kolmer according to method of E. C. Rosenow (Pneumococcus, Anaphylaxis, and Immunity, Jour. of Infectious Diseases, 1911, ix, 190).

[4] Product prepared by Prof. T. B. Osborne and H. G. Wells, obtained through latter.

	Time.	Blood.	Liver.	Kidney.	Mode of injection.
Pigs, Group 1	24 hours	0	+	++	Intraperitoneal
Pigs, Group 2	24 hours	++	+++	+	Vein
Pigs, Group 3	48 hours	+++	+	0	Intraperitoneal
Pigs, Group 4	48 hours	+	++	0	Vein
Pigs, Group 5	72 hours	0	0	0	Intraperitoneal
Pigs, Group 6	72 hours	0	0	0	Vein

Series IV. Same as Series III except that horse serum (10 c.c.) was used instead of egg-white.

	Time.	Blood.	Liver.	Kidney.	Mode of injection.[1]
Pigs, Group 1	24 hours	++++	+	++	Vein
Pigs, Group 2	48 hours	++	+	+	Vein
Pigs, Group 3	72 hours	+	0	++++	Vein

These experiments give somewhat irregular results, but in general they indicate that sensitization is dependent on the egg albumen content of the blood rather than on a retention of egg albumen in the tissues of the organs. The irregularities in both series are difficult to explain, but such irregularities are not infrequent in sensitization experiments.

To settle the question of blood content *versus* organ fixation the experiments summarized in Series V were undertaken. In these the sensitizing power of the blood of a rabbit was compared with the same power of extracts of the washed and unwashed kidneys. The method was as follows: Under the ether anesthesia a rabbit was bled from the carotid artery to secure 5 c.c. of defibrinated blood; the abdomen was then opened, and the vessels of one kidney ligated, and the other kidney was washed out through a cannula in the aorta with about 1000 c.c. of physiological salt solution. Pigs were sensitized with the blood from the carotid and with extracts of the two kidneys.

Series V. *Egg-white. Comparison of Sensitizing Power of Blood and Washed and Unwashed Kidney.*

	Time.	Blood.	Unwashed kidney.	Washed kidney.	Mode of injection.
Pigs, Group 1	24 hours	++++	+++	+	Vein
Pigs, Group 2	48 hours	+++	+++	+	Vein
Pigs, Group 3	72 hours	++	++	0	Vein
Pigs, Group 4	96 hours	0	++	0	Vein

[1] In this and most of the experiments which follow the administration of the intoxicating dose by intra-abdominal injection was abandoned on account of the more definite results obtained by the intravenous method.

These results are conclusive. In the normal animal the power of sensitization depends on the egg albumen content of the blood and not upon a peculiar fixation of the foreign protein in the kidney. It does not necessarily follow that the same is true for all protein substances, but these observations nevertheless tend to support the view that injury to the kidney by a particular substance is coincident with the period of elimination of that substance by the kidney, and not to a fixation in the parenchymatous cells.

Another problem, however, remained. Is a foreign protein eliminated as readily by the diseased kidney as it is by the normal kidney? This problem could perhaps have been more exactly solved if the experiments had been made on animals with a chronic renal lesion, but the difficulty of producing the latter with any degree of constancy, compelled the use of animals with acute lesions due to uranium nitrate or to potassium chromate.

The results obtained with three different groups of rabbits suffering from nephritis due to uranium nitrate are combined in the table which follows:

Series VI. *Power of Sensitization of Kidney Extracts of Animals with Uranium Nephritis Receiving Egg Albumen.*

Each rabbit received 0.0075 or 0.015 gram uranium nitrate subcutaneously; after twenty-four hours when coagulable protein was demonstrable in the urine, each received in the ear vein 10 c.c. egg albumen diluted with 30 c.c. salt solution; other procedures as in earlier experiments.

	Time.	Mode of injection.	Result.
Pig 1	24 hours	Abdomen	+++
Pig 2	24 hours	Vein	++++
Pig 3	48 hours	Vein	0
Pig 4	48 hours	Abdomen	0
Pig 5	48 hours	Vein	0
Pig 6	48 hours	Abdomen	0
Pig 7	48 hours	Vein	++++
Pig 8	72 hours	Abdomen	++
Pig 9	72 hours	Vein	++++
Pig 10	72 hours	Vein	++++
Pig 11	72 hours	Vein	++++
Pig 12	72 hours	Abdomen	+
Pig 13	72 hours	Vein	++
Pig 14	96 hours	Abdomen	0
Pig 15	96 hours	Vein	0
Pig 16	96 hours	Vein	0

These results are in general similar to those obtained in normal animals, but with a greater tendency to sensitization by the third day extract. (Compare Series I, III and V.) An acute nephritis due to uranium nitrate apparently lengthens slightly the period during which the kidney (or blood ?) may retain a foreign protein. The difference is, however, slight. No explanation is at hand for the curious negative results in four of the five experiments with forty-eight-hour extracts.

In another experiment, potassium chromate was used as the renal irritant, and the guinea-pigs were sensitized as in Series V, with blood and the extracts of washed and unwashed kidneys.

Series VII. *Comparison of Sensitizing Power of Blood and Extracts of Washed and Unwashed Kidneys of Chromate Nephritis with Egg Albumen Injection.*

Each rabbit received 0.3 gram potassium chromate subcutaneously, and on the following day, after coagulable protein had been demonstrated in the urine, received in the ear vein 10 c.c. egg-white diluted with 30 c.c. salt solution. Blood was drawn and extracts of washed and unwashed kidney were made after one, two, three, four, and five days. All intoxicating doses were given intravenously.

	Time.	Blood.	Unwashed kidney.	Washed kidney.
Pigs, Group 1	24 hours	++++	++++	++++
Pigs, Group 2	48 hours	+++	++++	++
Pigs, Group 3	72 hours	++	++	+
Pigs, Group 4	96 hours	++++	+++	+
Pigs, Group 5	108 hours	0	++++	0

Here we have definite evidence of a persistence of the egg albumen in the blood as shown by the sensitizing power of the blood and of the extracts of unwashed kidney on the fourth day, a period greater by forty-eight hours (see tables I, III, and V) than in the normal animal. The discordant result with the unwashed kidney extract of the fifth day cannot be explained; it is in keeping with the irregular results seen in other series, as in III, IV, and VI. These irregularities are due in all probability to the variations in the susceptibility of the guinea-pig to sensitization or possibly also to variations in the power of the rabbits to eliminate a foreign protein. This variation in results is the one weak point of this

investigation. However the results in general hold together, and a comparison of normal animals with those having nephritis shows that in nephritis there is a delay in elimination of about twenty-four hours to forty-eight hours, which is too constant to be dependent upon the experimental error of the method employed.

Discussion. This investigation has been based on the assumptions that parenterally introduced protein is removed in part by the kidney unaltered, is in part destroyed (digested ?) within the tissues, and that the power of the blood or of an extract of the kidney to sensitize to a certain protein is evidence of the presence of that protein in the blood or kidney used for sensitization. With this goes the parallel assumption that until the protein is all digested or removed it is being eliminated by the kidney, and that therefore the period of its persistence in the kidney can be determined by sensitization tests. That the egg albumen actually is eliminated by the kidney and occurs in the urine in a form, and in sufficient amount, to sensitize guinea-pigs is shown by the following experiment. Ten c.c. of egg albumen diluted with 0.85 per cent. salt solution were injected into the ear vein of a rabbit, and six hours later the urine of the animal was obtained by catheterization. Each of three guinea-pigs received 2 c.c. of this urine intra-abdominally. After twenty-four hours the animal was again catheterized and the same amount of urine was injected into each of a group of three pigs. Nine days later one pig of each group received in the jugular vein 1 c.c. of egg albumen diluted with salt solution. The disturbance which resulted was of slight severity and of doubtful significance. At the end of three weeks, however, a similar treatment of the four remaining pigs resulted in typical symptoms and the death of all the pigs, which on autopsy showed the characteristic lungs of anaphylaxis. There can be no doubt, therefore, that in the rabbit the intravenous introduction of egg albumen is followed by its elimination by the kidney in a form capable of causing sensitization. No attempt has been made to determine for how long a time the sensitizing power of the urine persists.

From another side, however, there is considerable evidence that the larger part of the injected egg albumen is eliminated with the urine during the first forty-eight hours after injection. Thus

in the urine of the first day, and to some extent in that of the second day, there appears on heating either a solid clot or a heavy, coarse, flocculent precipitate, which settles rapidly and is quite different from the fine, granular, slowly settling precipitate of the serum proteins of nephritis. After forty-eight hours little or no precipitate is obtained. The possibility that the coagulable protein is in part composed of native serum albumin cannot be denied, but the prompt disappearance of coagulable protein after forty-eight hours is not characteristic of any known acute experimental nephritis giving so large a precipitate in the first twenty-four hours. As normal urine has the power through its non-coagulable protein content, according to Wells and others, to sensitize guinea-pigs to serum proteins, the anaphylaxis reaction for such proteins cannot be used as a differential control, and has therefore not been attempted in this investigation.

It has been assumed, therefore, that most of the coagulable nitrogen of the urine after intravenous injection of egg albumen is indeed egg albumen, and in order to determine the rate of its elimination, for comparison with the sensitization tests, determinations of the total nitrogen of the egg-white mixture injected and of the coagulable protein of the urine have been made.

The following experiment is illustrative:

A rabbit received in the ear vein on April 26, 40 c.c. of a 1 to 3 mixture of egg albumen. The nitrogen of 40 c.c. of this mixture as estimated by the Kjeldahl method was 0.191 grams.

Nitrogen in coagulable protein of urine of first period of 20 hours	0.096 gram
Nitrogen in coagulable protein of urine of second period of 28 hours	0.0441 gram
Nitrogen in coagulable protein of urine of third period of 24 hours	0.0054 gram
Nitrogen in coagulable protein of urine of fourth period of 24 hours	0.005 gram

Other observations follow:

I.	Total nitrogen in 40 c.c. egg-white dilution (10 c.c. egg-white)	0.178 gram
	Nitrogen in coagulable protein of urine of first 48 hours	0.094 gram
	Nitrogen in coagulable protein of urine of second 48 hours	0.017 gram
II.	Total nitrogen in 40 c.c. egg dilution	0.177 gram
	Nitrogen in coagulable protein of first 48 hours' urine	0.106 gram
	Nitrogen in coagulable protein of second 48 hours' urine	0.004 gram

It is impossible to say that the coagulable protein of the urine does not contain serum protein, but its prompt decrease after

forty-eight hours favors the supposition that it is mainly egg albumen. If this interpretation is correct, considerably more than one-half is eliminated within forty-eight hours, and only very small amounts during the third and fourth day; the remainder is, presumably, digested or otherwise changed in the animal tissues. Thus the evidence concerning the elimination of egg-white obtained in this way supports the results of the sensitization experiments for the stronger anaphylaxis was always obtained with the first and second day extracts and the weaker reactions and failures, with extracts representing later periods.

In connection with the question of possible sources of error in these experiments another question arises, that of the effect of foreign protein on the normal kidney. If egg albumen is toxic to the cells of the kidney the experiments here described as demonstrating elimination in normal animals are really experiments on animals with injured kidneys. Vaughan, it may be remembered, believes that the kidneys of animals receiving egg-white are seriously injured. In the present investigation histological examination of the kidney has been made only when an animal died before the regular periods set for making extracts. In several instances a definite exudate about the glomerular tuft, markedly distending Bowman's capsule, has been seen. Whether this represents an exudate of serum albumin or the foreign egg albumen coagulated by the fixing agent we have found no means of determining. The prompt disappearance (after forty-eight to seventy-two hours) of coagulable protein from the urine has, however, seemed to indicate that the kidney is not seriously injured by a single injection, and that the fine granular precipitate in the glomerular spaces is therefore in all probability egg albumen.

SUMMARY. Extracts of the kidneys of normal rabbits prepared one, two, three, and four days after the intravenous injection of egg albumen and horse serum have the power to sensitize guinea-pigs to a second injection of these proteins; the sensitization by first and second day extracts being constant and of intense degree, that by the third day extract less marked or sometimes absent, and by the fourth day extracts only occasional and always weak.

Comparative studies of the power of the blood, liver, and kidney

to sensitize, indicate that this sensitization depends on the content of foreign protein in the circulating blood and not upon its accumulation or fixation in the tissues of an organ. This opinion is supported by other experiments in which the sensitizing power of the blood and of the extracts of unwashed kidneys was compared with the sensitizing power of extracts of washed kidney.

The weak sensitizing power of washed kidney extract is taken as evidence that foreign proteins of the kinds used are not held into the tissues of the kidney, and if these results may be applied to nephrotoxic proteins it follows that nephritis is not due to selective and persisting fixation of a protein by the renal cells, but is due to the action of such protein merely during the process of its elimination.

In experimental acute nephritis of the type due to uranium nitrate, the power of sensitization to egg albumen is prolonged for twenty-four hours and in the chromate type for forty-eight hours, thus indicating that in nephritis, of the acute type at least, the elimination of a foreign protein is delayed.

Attempts to study by the same methods the elimination of vegetable and bacterial proteins have failed.

DISCUSSION

Dr. M. J. Rosenau: It seems to me very clear that this protein matter, as has been pointed out by Dr. Pearce, is in the blood rather than fixed in the tissues of the liver and kidneys. The work interested me from the standpoint of using anaphylaxis as an instrument. I am prompted to throw out the caution that we have as yet no criterion of determining when anaphylaxis is present or absent. The methods so far are crude. There must be evident indications on the reacting pig before we can say whether the reaction has occurred or not. That is one point in this particular biological phenomenon which needs to be cleared up in order to make it a more delicate means of determining some of these things for which the reaction is used. Further, it is not a quantitative test at all, merely a qualitative test. We must depend upon mass action. A positive result upon one guinea-pig is of little value; a negative result still less.

Dr. L. F. Barker: The experiments are very interesting as throwing light on the time required by the protein to go through the kidney. In the normal kidney the length of stay in the epithelium is evidently very short. In some of the nephritic kidneys it was apparently retained longer. That might be due either to delayed passage through the epithelium, or to retention, after secretion, in the tubules, inasmuch as washing out the bloodvessels would not wash out the tubules. It is exceedingly interesting that experimental physiologists have found that the kidney is able and, as it were, eager quickly to rid the blood of foreign proteins. Thus it has been shown that egg albumen, bacterial proteins, and free hemoglobin are excreted. The experimental studies of J. E. Schmidt, especially, are interesting in connection with these studies of Dr. Pearce.

Dr. Pearce: There is, in reply to Dr. Barker, one other possibility. Not infrequently the glomerular capsule is seen on histological examination to contain a coagulum. This may be serum albumin or it may be egg albumen in the process of elimination. It is impossible to say which. It obviously cannot be washed out, and if it is egg albumen, explains perhaps the frequent sensitization in late periods of nephritis.

BENCE–JONES PROTEINURIA: A REPORT OF FOUR CASES, WITH SOME CHEMICAL AND BIOLOGICAL NOTES

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1. *Introduction.* Having had the unusual opportunity of studying, with more or less completeness, 4 cases of Bence-Jones proteinuria, it seems to the writers worth while to record these briefly with some observations on the methods of recognition, chemical properties of the body, and certain biological reactions. The work of Magnus-Levy,[2] Grutterink[3] and de Graaf, Abderhalden and Rostoski,[4] and especially the recent exhaustive contribution of Hopkins and Savory,[5] have made it certain that this body is not an albumose, but a true protein, yielding the characteristic amino acids on hydrolysis. The theories as to its origin are quite numerous, but in the light of the more recent investigations the more important are those which seek derivation (1) from the proteins of the tissues or blood, (2) specifically from the tissues of the bones, or (3) as a product of abnormal protein metabolism, either endogenous or exogenous. Of these the preponderance of evidence seems to favor the idea that the enormous output of the protein is rather due to the influence of the tumor, or its products, on the tissue metabolism, than the direct product of a relatively small amount of tumor substance present in the body. The great majority of the cases in which this body has been found in the urine have been instances of multiple myeloma, although not all individuals suffering from this disease have exhibited Bence-Jones proteinuria. In isolated instances it has been found associated with other pathological conditions, such as leukemia, chloroma, lymphosarcoma, tuberculous osteoarthritis,

myxedema, and carcinomatous metastases (1 case). It is also to be noted that some of the reported occurrences associated with leukemia and osteomalacia were subsequently found to be cases of multiple myeloma. The most complete historical review which has come to our notice is that of Rosenbloom (*Biochemical Bulletin*, 1911, i, 161 to 173)

2. Case Reports:

Case I.—C. F., white, female, aged fifty-four years. Patient of Prof Gordon Wilson, Baltimore.

Complaint: Rheumatism. Family history unimportant; past history: intermittent fever at twenty. At twenty-six fell and hurt left leg, which two years later broke down and ulcerated. Treated several years in the Johns Hopkins dispensary. Normally well until October, 1909, when she began to have pains in left leg which extended to her back and neck, and developed swellings, considered to be rheumatic, in feet and legs, which gradually involved larger joints of arms as well. In the winter of 1909 began to have gastric disturbance, regurgitation of food, not much nausea, no hematemesis, great wasting. Was considered to have carcinoma of the stomach. Became bedridden, owing to joint troubles and weakness. May, 1909: severe pains, worse at night, often lancinating in character, in both arms and legs. Gradual atrophy of muscles and stiffness. Severe diarrhea developed in summer of 1910, with abatement of gastric symptoms. Frequent small mucous stools, but no blood. At times incontinence of feces. In the fall and winter of 1910–11, had increasing polyuria, with cystitis. Bence-Jones protein was found in the urine by Dr. Wilson in January, 1911; it had not been observed in the last previous examination, October, 1910.

Patient was first seen by us January 20, 1911, at which time she showed great emaciation and rigidity of the extremities. Pupillary reactions normal. There was a moderate stomatitis, with some salivation (not due to mercury). Tongue very thick, pallid, with marked hypertrophy of the papillæ. Buccal mucous membrane opaque and soft. No abnormality in lungs. Heart slightly enlarged; showed a well compensated mitral stenosis and insufficiency. Peripheral arteries sclerotic. Pulse good volume, regular, 80. Blood pressure, systolic, 110 to 120 mm. Hg. Abdomen scaphoid. No abnormal pulsation or peristalsis. No masses made out on palpation. Pelvic organs apparently normal. Extremities: marked thickening about large joints, with limitation of motion and pain on manipulation. No acute inflammatory changes. Terminal phalanges of fingers and toes somewhat enlarged and clubbed. Left tibia was distinctly enlarged throughout greater part of shaft, but not rough or irregular. No enlargement of ribs or bone tenderness there or elsewhere in skeleton made out.

Rather marked diffuse keratosis in palms and plantar surfaces of feet. Patient was subject to occasional syncopal attacks in which she apparently had very weak pulse, without convulsions. Marked cutaneous hyperesthesia on palms and soles of feet. At this time there was polydipsia and polyuria. Blood: rather marked secondary anemia. Normal white blood count and differential. *Wassermann:* negative. *Urine:* amount twenty-four hours, 2350 cc., pale yellow, cloudy, faintly alkaline. Specific gravity, 1014. Heavy white sediment of granular debris, epithelial cells. No casts, blood, or pus. No sugar. Biuret reaction positive. Abundant carbonates. Uric acid, 0.54 gm. Total nitrogen, 12.68 gm. Total chlorides, 2.3 gm. (During the last few months of life it was impossible to secure a twenty-four hour-specimen, but total amount of urine was about 500 c.c. per day, giving a total chlorides of 3 gm.) Polarization after removal of protein negative. Diacetic acid and acetone absent. Urobilin present. Total protein 2 gm. to liter (Tsuchiya). Heller's HNO_3 test heavy white ring at contact line. With heat and acetic acid the protein precipitated between 56° and 60° C. Partial resolution on boiling and reprecipitation on cooling. Filtrate gave no biuret or Adamkiewicz tests. With dilute HNO_3 (25 per cent.) characteristic precipitation in the cold with nearly complete solution on boiling and reprecipitation on cooling.

The case was observed at intervals until her death, May 6, 1912. The polyuria disappeared, partly owing to increasing stomatitis and difficulty in swallowing. Tongue became so large as to practically fill the mouth, deep red in color, marked superficial maceration. In December, 1911, patient was seen again after four months, when a nodule was noted on anterior border of left scapula, very hard, and apparently continuous with the bone. This gradually increased, reaching the size of a hen's egg before death. In February, 1912, there was tenderness over the third and fourth ribs, left precordium and axilla, but no nodules were made out. This persisted and increased, ribs becoming eventually definitely nodular and, six days before death, they caved in. Coincidentally with this there developed a pericardial friction rub of great intensity with extreme pain. There was tenderness over most of the thoracic spine, but no nodes were discovered. In April, 1912, nodules were noted over anterior surface of both elbows about the condyles; there was a brawny induration of the fingers, very like scleroderma with an extraordinary overgrowth of the horny layers of the skin and a hypertrichosis of the hairs of the face. At this time there was noted a mass extending from the anterior superior spine of the ilium on the left side, half-way to the pubis, which was firm, elastic, and exquisitely sensitive. It caused great pain, referred to the distribution of the anterior crural nerve. A similar, but smaller, mass was felt just behind Poupart's ligament on the right side, near the pubis. These, with the nodules on the other bones, increased with great rapidity during the last four weeks of life, the one on the left ilium reaching the size of a large

orange. The inguinal, axillary, and epitrochlear glands became enlarged during this period; were discrete, firm, and sensitive to the touch. The patient lost all ability to swallow, apparently owing to the enormous swelling of the tongue. Articulation was much impaired. She took no food or water during the last week of life.

X-ray examination, made in February, 1912, with a portable apparatus, was unsuccessful with the exception of the plate of the left tibia, which showed an enlarged, swollen tibia. "There were no absolute areas of bone destruction, but there was a laminated rarefaction, extending throughout the tibia. From the *x*-ray examination it would be impossible to state definitely that this change was myeloma. In fact, the bone changes simulate more closely the changes one sees in Paget's disease."

No autopsy was permitted.

During the entire period of observation (fifteen and one-half months) the urine showed constantly a reaction for Bence-Jones protein.

Case II.—C. G., white, male, aged fifty-two years. Patient of Prof. H. G. Beck of Baltimore, who kindly gave us his notes and a specimen of urine after the death of the patient, January 7, 1912.

Abstract of Dr. Beck's notes: "Patient was first seen September 8, 1911. Has been ailing for some months. Complained of shortness of breath, poor memory, weakness, and loss of weight. Physical examination showed arteriosclerosis, hypertrophied heart, aortic and mitral regurgitation. Blood pressure 215 mm. Hg. Urine gave a large precipitate with acetic acid and potassium ferrocyanide, but none by heat. September 15: urine contained a large amount of albumose, but no serum albumin. October 17: urine showed precipitate with acetic acid and potassium ferrocyanide, but none on boiling. December 2: an attack of acute paroxysmal pulmonary edema. Very cyanotic. Frothy serous expectoration. These attacks have been noted several times in last four years, occurring at night and lasting several hours. December 10: urine showed (1) an opacity at 50° C., precipitate at 70° C., partial clearing on boiling; (2) complete precipitation with two volumes of saturated ammonium sulphate solution; (3) no precipitate in cold with acetic acid. December 18: examination of chest shows small elevations on ribs almost nodular, but no tenderness. *X*-ray of chest does not show any bony changes. December 23: differential leukocyte count normal. Hemoglobin, 58 per cent. January 7, 1912, patient died suddenly after being out all day, apparently of acute dilatation. No autopsy was secured."

Specimen of urine submitted for our examination by Dr. Beck showed characteristic reaction for Bence-Jones protein: precipitation with heat and acetic acid between 54° and 60° C., partial clearing on boiling, reprecipitation on cooling. Filtrate yielded no test for protein. Typical reactions also obtained with 25 per cent. HNO_3 and on addition of two volumes of saturated solution of ammonium sulphate. Urine clear, acid,

specific gravity 1013, no sugar. Total protein 1½ grams per liter (Tsuchiya.) Total chlorides 5 grams per liter. No casts.

Case III.—S. S., white, male, aged sixty-four years. Patient of Dr. Henry M. Fitzhugh, Westminster, Md. Admitted to the Johns Hopkins Hospital January 9, 1912, under the care of Prof. T. B. Futcher.

Complaint: Pain in left lumbar region and at the navel.

Family History. Unimportant.

Personal History. Unimportant.

Present Illness. Began about two months ago, pain on left side under costal margin, worse in afternoon and at night. Eructation, no vomiting, no blood in stools.

Physical Examinations. Large man, undernourished, slightly anemic. Pupils react normally. Thorax symmetrical. Lungs clear. Heart normal. Pulse normal. No marked peripheral sclerosis. Blood pressure 180 mm. Hg. Abdomen: no abnormality other than palpable right kidney. Rather marked dermatographia. Exaggeration of deep reflexes. No general glandular enlargement. No enlargement or nodes noted over long bones or ribs. Tenderness over eleventh and twelfth ribs, on left side. Patient thinks he may have injured this side some six months ago.

Ewald test meal: showed marked hyperacidity.

Blood: red blood corpuscles, 3,800,000; white blood corpuscles, 14,000; Hemoglobin, 55 per cent. Differential shows increase in polymorphonuclear neutrophiles.

X-ray: "Lumbar spine negative. Ribs show small vacuolated areas; similar areas in right humerus, due to bone destruction. These areas are sharply defined and there is slight new bone formation around the edge, showing an attempt to limit the disease."

Urine gave characteristic precipitation at 54° C., complete at 60° C., partial clearing on boiling, reprecipitation on cooling. Filtrate free from protein. Precipitate insoluble in water, but readily soluble on heating with dilute sodium carbonate solution, latter removed by dialysis, leaving the protein in solution. With 25 per cent. HNO_3 precipitation in cold, almost clear solution on boiling, reprecipitation on cooling.

During twenty days of the patient's stay in the hospital the total daily amounts of urine were examined. The Bence-Jones protein was constantly present and was the only protein demonstrable. The total amount of urine varied between 2000 and 2800 c.c. Specific gravity, 1006 to 1010. Total protein, 5 to 7 gm. (Tsuchiya). Total chlorides varied from 1½ to 4½ grams. Coarsely and finely granular casts were found at each examination.

Patient lived about thirteen weeks after leaving the hospital, all the urine being saved and sent to the laboratory, where examination showed the constant presence of the Bence-Jones protein and no other. He grew steadily feebler with increasing pain, referred to ribs on left side. Toward

the end there was a development of nodes along the ribs over precordium, with falling in of the sternum, and great pain on breathing and coughing. There was enlargement of the lymphatic glands in the right groin with great pain in the distribution of the anterior crural nerve.

No autopsy was permitted.

Case IV.—E. B., white, female, aged thirty-seven years. Admitted to the Johns Hopkins Hospital April 22, 1912. Died May 9, 1912.

Complaint: Rheumatism.

Family History. Father supposed to have died of cancer.

Personal History. Unimportant.

Present Illness. Began six months before admission with onset of sudden pain in right hip which increased so that she was obliged to stop work two weeks later. Walked with great difficulty. After two months a similar trouble appeared in left hip. Coincident with the joint trouble she noticed increasing nervousness, numbness of hands, and awkwardness. Appetite poor, occasional vomiting unassociated with pain. Loss of forty pounds in weight. Four weeks ago noticed a lump in right breast where she had some pain. Discovery of this lump not elicited in taking history, but during physical examination.

Physical Examination. Patient much emaciated. Slight general pigmentation, most marked in folds of the skin. Mild grade of ichthyosis simplex. Pupils react normally. Lungs clear. Heart normal. Hard irregular mass in right breast with retraction of nipple and some puckering of the skin. Abdomen normal. Reflexes normal. No local or general glandular enlargement. Spine somewhat stiff. Some shortening of the right leg. Tender nodes on sixth rib, right side, below breast. Blood pressure 140 mm. Hg.

Blood: red blood corpuscles, 4,000,000; white blood corpuscles, 9200. Hemoglobin, 74 per cent. Differential normal. Wassermann: negative.

"*X*-ray examination shows carcinomatous metastases in head, ribs, both trochanters, both ilia, and right tibia. These metastases are slightly different from what one sees in simple, ordinary metastases, in that the areas involved in the bones are sharply limited, and do not seem to be invasive in character, as one generally sees. The metastatic areas in the bone, at first glance, present the appearance more of a giant-cell sarcoma, as there is definite new-bone formation around the edge, showing an attempt had been made to limit the disease."

Urine: acid, clear, 1012 to 1018. No sugar. No casts. With heat and acetic acid there is a precipitation at 60° C., partial clearing on boiling, reprecipitation on cooling. Filtrate from this reaction gave no tests for protein. Total amounts of urine were studied for nine days, up to forty-eight hours before death. From the combined urines of this period the Bence-Jones protein was isolated by precipitation with two volumes of saturated ammonium sulphate and dialization until free from salt, the

process being repeated three to four times until a clear, neutral, slightly amber colored fluid was obtained which gave all the characteristic reactions for Bence-Jones protein in the pure state. This case will be reported in detail elsewhere.

The patient became rapidly weaker and semicomatose with loss of control of sphincters, difficulty in swallowing, feeble, irregular heart, death occurring on May 9. No autopsy was secured, but a portion of the femur was removed for section.

"Section of bone and tumor showed epithelial cells of the glandular type in alveoli of different sizes and shapes, surrounded by a rather dense fibrous stroma. In this stroma there are two types of bone areas, old bone showing lacunar absorption by the cancer cells and typical islands of new-bone formation of the endosteal cell type. This was first described by von Recklinghausen as ostitis carcinomatosa."

3. *General Consideration of the Urine.* As has been so clearly demonstrated by Hopkins and Savory, the specificity of the reaction for Bence-Jones protein is dependent upon the relative stability of its compounds with neutral salts at the boiling temperature and their instability at lower temperatures (45° to 60° C.). The saline concentration has a marked influence on the completeness of the reaction, following closely the laws defined by Hardy for globulins, but differing essentially in the temperature relation. Salts are similarly graded for Bence-Jones protein at 100° C. and for globulins at room temperature. It follows from the above consideration that in applying the heat and acid test to urine for the detection of protein, it is important to heat slowly in order that the differences of temperature in the determination of precipitation may be apparent. Should coagulation begin well below the boiling point, more careful examination for the detection of unusual proteins (fibrinogen or Bence-Jones protein) are indicated. If this principle were impressed on students in their training, there is little doubt that many cases would be detected which are otherwise overlooked. In such instances of precipitation well below the boiling point, careful note should be made of any tendency toward clearing on boiling the specimen and the test repeated with the aid of a water bath and a thermometer. Confirmatory tests are made by treating another specimen with a few drops of 25 per cent. HNO_3, when the initial turbidity in the cold is increased as we approach 60° C. and clears up more or less

completely at 100° C., falling out again as the specimen cools. For further confirmation another specimen is treated with two volumes of saturated ammonium sulphate solution when a voluminous precipitation occurs, sometimes quite slowly. These tests are sufficient to establish the presence of Bence-Jones protein. Other tests for Bence-Jones body as it occurs in the urine and when isolated in the pure state may be found on reference to table in Neuberg *Der Harn*, 1911, i, 774. If serum albumin is also present, it may be determined by first heating the acidified urine to 60° C. for one hour, cooling, filtering until perfectly clear, and boiling the filtrate.

At the outset of this investigation it was our intention to repeat the work of Magnus-Levy, Grutterink and de Graaf, and Abderhalden on the chemical constitution of the body isolated from our abundant material, but this field has been so satisfactorily covered by Hopkins and Savory as to render it unnecessary. A few notes may be made, however, on the relative advantages of the various methods of quantitative separation. For securing material without denaturing the protein, the salting with ammonium sulphate, dialyzing the precipitate, and repeating the process many times, probably yields the best result. This method has the objection that it is time-consuming and does not free the protein from pigment.

It has been our experience that the urines containing this protein become very dark on standing, even when preserved from putrefaction, and great difficulty was experienced in obtaining any precipitate which was not deeply pigmented. Various attempts were made to decolorize the urine before precipitating the protein by use of animal charcoal, Kieselguhr, or carbon black, but we could find no method which yielded a colorless filtrate which did not at the same time remove the greater part or all of the Bence-Jones body. Precipitates treated in thin dialyzing sacs of collodion with running water for weeks held tenaciously to the coloring matter. We also found, as has been noted by other observers, that the protein, when dried *in vacuo*, becomes very dark, and these dried precipitates, in our experience, were never completely soluble in distilled water, which we consider an evidence of partial denaturization.

The alcohol precipitation would seem to be limited in its applica-

tion to the treatment of small volumes which may be rapidly handled, as the protein soon passes into an insoluble condition on prolonging its contact with the alcohol. Perhaps, where facilities for refrigeration, on a large scale, are available, the usefulness of this method may be extended.

For purposes of chemical analysis, when the denaturization, due to heating, is of no moment, we have devised a method which gives excellent results, especially in freeing the substance from pigment and leaving it as a fine dry powder.

The urine is filtered through paper, faintly acidulated with acetic acid, and placed in large bottles in the water bath, which is kept at 60° C. over night. On removal from the bath, the greater part of the coagulum has settled to the bottom of the containers, which permits of decantation, or siphonage, of most of the supernatant urine. The precipitate is then repeatedly washed in the bottle by shaking with distilled water, and finally collected on a filter and the washing continued until the filtrate is free from chlorine. The wet precipitate is then spread in Petri dishes in layers not more than 0.5 cm. thick, sealed, and placed in a freezing mixture of ice and ammonium chloride. The frozen material is rapidly transferred to a desiccator, packed in a freezing mixture. The desiccator is then quickly exhausted to a vacuum of 4 mm. or less, when the ice in the precipitate sublimes and is absorbed by the H_2SO_4, leaving the precipitate as a dry, crumbling mass, pale gray to white in color, which is easily pulverized. This material is insoluble in water but readily dissolves a dilute solution of sodium carbonate on heating, yielding a water-clear solution from which the sodium carbonate can be easily removed by dialysis, leaving the protein in solution. Such a solution gives all the characteristic reaction for Bence-Jones protein in the pure state. Many attempts were made to crystallize the substance following the methods of Grutterink and de Graaf and Magnus-Levy but none was successful.

In Case I, longest under observation after the recognition of the proteinuria, the amount excreted varied from 2 to 5 grams per liter with an output of 2 to 3 liters in twenty-four hours. In Case III the amount reached as high as 7 grams per liter, with an output of urine about the same as in Case I. The smallest excre-

tion was in Case IV, in which the maximum was 1.5 grams per liter and the average 0.25 to 0.5 gram.

In one of our cases (I) we have observed spontaneous precipitation of the protein on standing for several months. These specimens of urine were found, on bacteriological tests to be sterile and the initial alkalinity considerably increased, though the urines were not ammoniacal. This phenomenon has been previously noted by Bradshaw[6] and Rosenbloom,[7] and will be reported fully elsewhere.

Polyuria was present at some time during the course of the malady in all of our cases except one (IV).

A striking feature to which attention has not heretofore been called is the great diminution in chloride excretion. The daily output in Case I was 2 to 3 grams; Case II, 5 grams; Case III, 1.5 to 4.5 grams; Case IV, 1.2 to 1.4 grams. In one Case (IV) careful functional tests were made by Drs. Fitz and Rowntree. These showed a phenolsulphonephthalein excretion of 23 per cent. for two hours, lactose 8 per cent., iodide present after seventy-two hours, total chlorides 0.15 to 0.18 per cent. of the amount ingested. In this case, also, serum albumin was at times present, but no casts were found. In the other cases the Bence-Jones body was the only protein present. In Case III casts were constantly present. None were found in Cases I and II.

4. *Biological Reactions.* Although the chemical side of the Bence-Jones protein has been fairly completely covered in recent years, the biological investigations have been meager and somewhat conflicting. Borchart[8] and Lippmann have reported the detection of the body in the blood and serum of fasting dogs fed with the substance. In an alkaptonuric patient Gross[9] and Allard noted a marked increase of homogentisic acid after feeding with this protein, in contrast to results obtained on feeding similar amounts of casein. After injection intravenously and subcutaneously, various authors have reported the presence of a specific precipitation in the serum or blood. Rostoski found the reaction did not differentiate the Bence-Jones body from other proteins of human origin. Hopkins and Savory concluded that it is less powerful as a precipitinogen than blood proteins, but that its

solutions reacted slightly with antihuman serum. Massini[10] reported complement deviation with highly potent sera and was able to differentiate between the blood proteins and the Bence-Jones proteins. Stokvis[11] noted the appearance of the protein in the urine of dogs after its injection intravenously or by the rectum. In our own experiments we have used the protein obtained by ammonium sulphate precipitation, and have been unable so far to secure a specifically active precipitin, finding only weak reactions of equal intensity for Bence-Jones, and human blood serum, but are continuing the experiments with larger doses and with the substance in various states. In all our rabbits, injected intravenously for the production of precipitins, there was commonly anuria for twenty-four hours, followed in some instances by the excretion of the protein in the urine in the next forty-eight hours; while after the second injection none of the animals excreted the protein as such.

Intradermal skin tests for sensitization were made, with the same lot of material used for other biological tests, with negative results. The test was applied to a considerable number of individuals, normal persons, and others with various pathological conditions, four of whom had bone metastases from carcinoma and sarcoma, inclusive of Case IV. Instillation of the solution into the conjunctiva of Case I did not produce a reaction, nor was any obtained in a case of multiple lymphosarcomatous metastases to the bones. Anaphylactic tests on guinea-pigs are in progress and other biological investigations with this protein have been undertaken.

5. *Summary.* From the fact that the writers have observed 4 cases in fifteen months, it would seem that this type of proteinuria is probably more common than the literature would lead one to suppose.

Of these cases 2 (I and III) were clinically multiple myeloma, and a third (II) was probably of the same origin, although we have no objective proof. The remaining case (IV) was one of metastatic carcinoma from the breast, and is, we think, unique, as the case reported by Oerum[12] was associated with metastases from a gastric carcinoma. This case will be reported in detail elsewhere. It is especially interesting to note that the detection of the last three

followed definitely the interest aroused among local physicians by the presence of the first case, which led them to test the urine of their patients more carefully. We should like to emphasize the fact that the recognition of the Bence-Jones body in the urine in each instance antedated any suspicion of the true nature of the malady, with the exception of Case IV, which was clearly associated with carcinomatous metastases. That this type of proteinuria may be present for some time before any clinical evidence of multiple myelomatosis appears is shown by the first 3 cases noted. In Cases I and III the palpable bone tumors developed only late in their course. In Case II death occurred from an intercurrent disease before the appearance of any symptoms suggesting bone involvement, and the skiagrams, taken twenty days before death, showed normal bone shadows. In Case I the *x*-ray pictures, as above noted, were imperfect. In Case III the radiologist made a diagnosis of an unfamiliar type of vacuolization in the bones prior to the appearance of any palpable bone tumors, while in Case IV an accurate diagnosis of metastatic carcinoma of the bones was made.

The blood picture in our cases showed nothing abnormal except a secondary anemia. All the patients were over fifty years of age except the case of carcinomatosis (IV). In all there was evidence of great metabolic disturbance in the extreme emaciation. Spontaneous fracture of ribs occurred in 2 cases. The development of metastatic nodes in the soft tissues, as in Cases I and III, is unusual in multiple myelomatosis. Both of these had also glossitis.

In connection with Case I, it is noteworthy that there was marked hypertrichosis, macroglossia, keratosis of the palms and soles, and scleroderma. These point to some disturbance of the internal secretions which may have been coincidental. Fitz[13] has reported, however, Bence-Jones proteinuria in myxedema.

With regard to possible changes in the kidney, we can say nothing from the morphological standpoint, as we had no autopsies, but would merely call attention to the striking fact that the kidney was permeable for the Bence-Jones protein, but held back serum albumin (except just before death in Case IV), and in all cases

there was a striking diminution in the chloride excretion. These would seem to indicate functional disturbance of the kidney rather than a true nephritis.

In closing, we take opportunity to express our thanks to Drs. Wilson, Beck, Fitzhugh, and Futcher for access to their cases, and to Professors Barker and Halsted for use of material in their services. Special thanks are due Dr. Baetjer for his interest in the radiographic studies and to Drs. Fitz and Rowntree for the functional tests.

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A STUDY OF PYLOROSPASM AND OF THE PANCREATIC FERMENTS IN INFANTS BY MEANS OF A SIMPLE DUODENAL CATHETER

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NEW YORK

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About a year ago an account of a duodenal tube for infants[1] was published. This tube was introduced by mouth into the stomach, and then passed through the pylorus into the small intestine. This result was readily accomplished, the tube taking about one-half hour to pass the pylorus. The radiographs which accompanied this article showed conclusively that the end of the tube lay in the duodenum and was not merely curled on itself within the stomach cavity. The duodenal tube consisted, in brief, of short rubber tubing, with a silver-plated, perforated leaden ball at the end, and was a modification of the Gross duodenal tube used for adults.[2] By means of this simple device it was possible, after some practice, to gain access to the duodenum in infants in almost every instance. This was the first conclusive proof that the intestine could be reached by this route in infancy. The principle involved in this manipulation was that of gravity, carrying the leaden ball to the pylorus, aided by the onward movement of peristalsis, which swept the ball through the pyloric ring, and thence into the intestine. Although this tube served its purpose, it has been discarded for one which is simpler, as well as more serviceable, which has afforded a ready means of studying the functions of the stomach and intestines from a new point of view.

In the course of various experiments it suggested itself to try

[1] A. F. Hess, Amer. Jour. Dis. Child., May, 1911, p. 360.
[2] M. Gross, New York Med. Jour., January, 1910.

whether we could obtain the same result by making use of the ordinary soft rubber Nélaton catheter, which is used so frequently in infants and in adults for the purposes of lavage and feeding. To our surprise it was found that this simple instrument can be passed readily from the stomach into the duodenum. It is indeed interesting and instructive to reflect that this catheter, which was introduced into the realm of pediatrics by Epstein in 1880 for the purpose of gastric feeding and investigation, has, in these many years, never been seriously thought of in connection with the diagnosis and treatment of pyloric conditions and of intestinal disturbances, subjects which have been considered of primary importance during this long period.

During this interval we have made use of this catheter, which may in this connection be termed an "infant duodenal catheter," for clinical and experimental purposes on many hundred of infants of various ages to study:

1. The diagnosis and treatment of pylorospasm,[1] and concomitant motor disturbances.

2. The pancreatic ferments of infants.[2]

3. Icterus neonatorum[3] and congenital obliteration of the bile ducts.[4]

4. The bacteria of the duodenum.[5]

In order to demonstrate beyond all doubt that the catheter gains access to the duodenum, we have once more resorted to radiographic pictures (Figs. 1 and 2), criteria which are at least open to doubt. From these pictures it will be seen that the tube is well within the intestine. It will be noted that the catheter does not take a direct course from the cardiac end of the stomach to the pylorus, but that just as in the case of the duodenal tube, previously described, on entering the stomach cavity, it makes a sharp bend to the left to the fundus, and then turns upon itself to the right to reach the pyloric opening. This has been its peculiar course followed in almost all radiographs. This novel and unexpected picture controverts the assumption first considered, to explain

[1] A. F. Hess, Amer. Jour. Dis. Child., March, 1912.
[2] A. F. Hess, ibid., October, 1912.
[3] A. F. Hess, ibid., May, 1912.
[4] A. F. Hess, Archiv. Int. Med., August, 1912.
[5] A. F. Hess, Jour. Infect. Dis., August, 1912.

the ease with which the pylorus is reached. It shows that this success cannot be attributed to the vertical position of the stomach in infancy, to the fact that the tube or catheter follows an almost

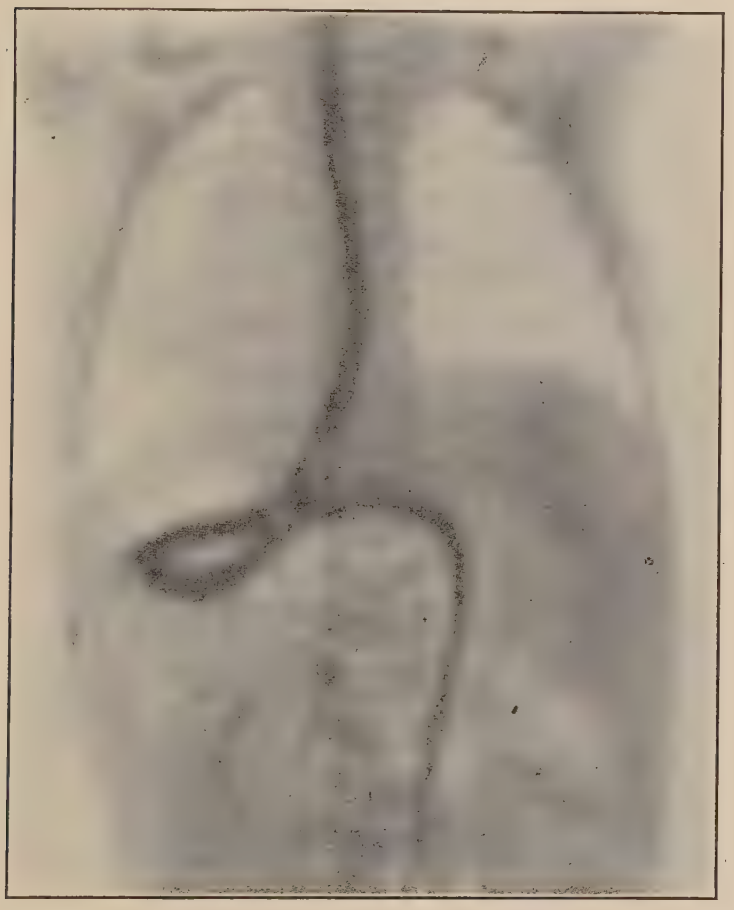

FIG. 1.—View from posterior, showing catheter well within the duodenum. Note the sharp turn to the left, to the fundus, which the catheter invariably takes on entering the stomach.

vertical course in its route to the small intestine, and has led us to attribute success rather to the diminutive size of the stomach cavity, and to a relative lack of tonicity of the pyloric ring. This explanation gains added weight from the fact that a catheter of

this kind cannot be used for this purpose in the adult, in whom the stomach is large, and the tube wanders far from the pyloric opening.

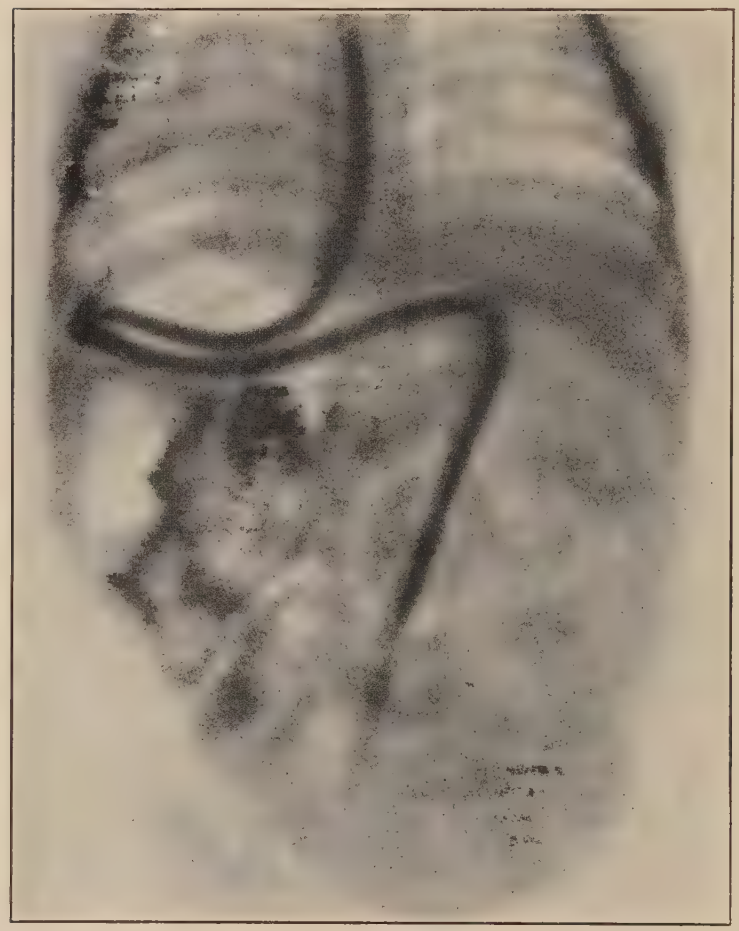

FIG. 2.—View from posterior. Duodenal feeding of three-months-old infant. Bismuth milk mixture in coils of intestine.

TECHNIQUE. It is difficult to describe the method of use of this simple instrument, for like all other instruments, even of a simple nature, its use can be learned only with some practice, and the

descriptions are far more complicated than the procedure would warrant. For the purpose an ordinary No. 15 (F.) soft rubber catheter should be employed, preferably one with a large eye; if the baby is very small, aged under a month, a No. 14 (F.) catheter should be made use of. Before beginning we should designate points 20, 25, and 30 cm. distant from the eye. This can be done by means of pen and ink. These markings allow us to take our bearings while introducing the catheter, and as long as it is in place. The catheter is now ready for use. The only other instrument necessary is an aspirator; for this purpose either the same

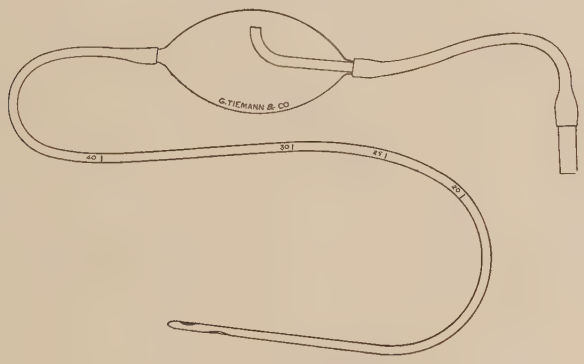

Fig. 3.—Catheter with aspirator.

aspirating bulb which I described in my previous article[1] may be used, or an ordinary aspirating syringe. The instrument is now complete (Fig. 3). The physician, therefore, generally has an infant duodenal catheter at hand, and needs but to acquaint himself with its use.[2]

The catheter is passed in the same way as the ordinary stomach tube; that is to say, it is lubricated with water, introduced into

[1] Loc. cit.

[2] Although a serviceable instrument can be prepared in this way by anybody wishing to make use of one, and a great deal of this work was carried out by means of a catheter which we happened to have on hand, nevertheless a catheter with two eyes at the tip, of exceptional length, and carefully marked, has additional advantages. The use of the bulb instead of an ordinary aspirating syringe has decided advantages; the greatest is that in aspirating through the bulb by means of the mouth one can in this way appreciate the amount of resistance offered by the stomach, or intestine, and thus gain valuable information as to the whereabouts of the end of the catheter. We should by all means urge anyone who intends to use this method frequently to make use of an aspirating bulb. The bulbs and the infant duodenal catheters may be obtained of Tiemann & Co., New York.

the mouth, and without the aid of the finger is rapidly pushed down the pharynx and esophagus into the stomach. It has seemed immaterial whether the baby is held in the sitting position, or lies upon its back, or upon the side. I have generally had it placed on its back with the arms bound snugly to its side by means of a towel. In a baby two months old, for example, when the 20 cm. mark is about 3 or 4 cm. from the gums, the contents of the stomach begin to be evacuated. The food is generally acid, and may contain free hydrochloric acid, as shown by its reaction to congo paper, if the feeding has been given some hours previously. After the stomach is empty, if we insert the catheter gently a little farther, we shall find no resistance until the 20 or 25 cm. mark is about at the gums, when a sense of obstruction may be felt, and the infant may gag, due to the contact of the end of the tube with the pylorus. While there is gagging or crying, accompanied by forced expiration, the catheter should never be advanced, for at this time the pyloric valve, and indeed the cardia as well, is constricted and prevents further passage. It we push on a little until we reach or pass the 25 cm. mark, we shall in most cases by this simple means have gained access to the duodenum. Indeed, there is no doubt, and a recent perusal of the literature confirms us in this opinion, that many have reached the intestine when they wished merely to enter the stomach, and the numerous reports supposed to record the capacity of the stomach, or to describe the nature of its contents, in reality combine data of the contents of this viscus and that of the upper part of the small intestine. When we consider also that pressure of the tip of the catheter upon the pylorus at times causes the pyloric valve to allow duodenal contents to pass into the stomach, there is further reason for believing that errors have crept in.

Naturally the first question is, "How do we know when we have reached the intestine, and why may not the catheter be curled on itself within the stomach?" Indeed, it is far easier to enter the duodenum than to learn the phenomena by which we may judge whether or not we have entered; however, the more experience we gain, the easier it becomes to judge of this point, and for some time we have rarely felt uncertainty in this regard.

There are several ways of ascertaining this fact. In the first place we must have an approximate knowledge of the distance of the pylorus from the gums or teeth. For example, this measurement for clinical purposes is about 20 cm. at one month, gradually increasing to about 25 cm. at a year.

Let us suppose that we are passing the duodenal catheter on a baby three months of age, and that we have gradually inserted it to the 25 or 30 cm. mark. We then halt, and watch to see whether the tube has a tendency to remain at this level or not. If you push a tube into the stomach, and have it coil up within its cavity, it will almost always, sometimes quickly, sometimes more slowly, the time depending on the fact of whether the child is quiet or gags and resists, work its way out of the mouth, so that the 20 cm. mark comes into view again. If, however, a tube has passed into the duodenum and is held by the pyloric sphincter, it will project almost vertically from the mouth and have a tendency, unless there is marked gagging, to hold its position, and not to work its way out again. This is an important, although not pathognomonic, sign of having reached the intestine. Frequently we are aided in obtaining our bearings by feeling the grip of the pylorus when we pull slightly on the catheter.

It might be thought that one of the most useful tests for orientation would consist in obtaining alkaline fluid or bile on aspiration, and most certainly if we obtain such fluids the evidence of success is convincing, and the gratification proportionately great. However, unless we are prepared to spend one-half hour, or an hour, or at times a still longer period, we may be unable to demonstrate our success in this manner. Nor is this necessary. The duodenal contents are frequently acid, and may continue to be so, due to the fact that gastric juice is being poured into the stomach and thence into the intestine. They may render it impossible to obtain alkaline juice, although the fluid may be golden yellow due to bile, and contain the various pancreatic ferments. Moreover, we may obtain a neutral or alkaline juice without any bile, as the bile is excreted intermittently, and often at long intervals. So that if we were to depend entirely upon the reaction of the fluid or upon its bile content, in judging of success in reaching

the intestine, we should often consider ourselves unsuccessful, whereas in reality we had reached the desired goal.

A test which is of value, especially in the beginning of the use of the catheter, is what may be called for the sake of brevity the "retraction test." By this is meant that when we are in doubt as to whether the catheter is in the stomach or the duodenum, we retract it very slowly, having an assistant aspirate through the bulb as we do so, until we have reëntered the stomach cavity. In this way, if the catheter has been withdrawn from the duodenum, one of two signs may be noted: either the assistant may note a marked change of resistance to aspiration, as the end of the catheter leaves the small constricted intestinal cavity and enters the stomach (and indeed frequently the assistant may give the first signal that the tube has left the intestine), or it may be noted by the sudden change in the nature of the juices obtained. Whereas, when the tube was in the duodenum a small amount of viscid fluid, neutral or somewhat acid, was being aspirated, or indeed no fluid could be obtained, when the tube is withdrawn to, let us say, the 20 cm. mark, suddenly there is a noisy gush of fluid of an entirely different nature, perhaps containing a marked admixture of foamy saliva, generally much larger in quantity, and frequently far more acid than that which had been obtained in the duodenum. As I have said, this test tells us whether the catheter was in the duodenum or not; however, it necessitates our making a second attempt to pass the pylorus. The more we use the tube the less we have to resort to this test.

Another test, but one of much less value, is what may be termed the "papillary bile test." This refers to the fact that sometimes when we withdraw the tube from the intestine toward the stomach, and reach the level of the papilla of Vater, there is a sudden gush of bile-stained fluid. This, however, is not usually the case, and the test cannot be relied on, but should be remembered, and made use of, in case this sign is noted in the course of the "retraction test."

Like most manipulations the passage of the duodenal catheter requires some practice and cannot be learned by description, but only by personal experience. After a few attempts the technique

has been fairly well acquired by hospital internes. The simplest methods of acquiring the technique is to pass the catheter in the way described, and control the result by means of the fluoroscope or radiograph. (The catheter casts a deep shadow without the aid of bismuth.) However, the *x*-ray is not absolutely necessary. Practice—far less practice than is required to master the technique of an otologic examination—is all that is required. Indeed, in very young infants it is difficult not to enter the duodenum if we do not push the catheter forward with too great haste. The younger the infant the easier is this accomplished. We have passed the catheter without difficulty on infants ranging in age from a few hours to one and one-half years.

In this paper in addition to describing a simple method of reaching the intestine in infants, a technique which seems to offer additional possibilities for diagnosis, for therapeutics, and for physiologic experiment, we wish to describe how this procedure has been of value in the diagnosis and treatment of some pathologic conditions encountered during the last few months

The Diagnosis of Pylorospasm. There is perhaps no group of cases more puzzling at times than that characterized by persistent vomiting. From day to day our diagnosis wavers among various possibilities: indigestion, pyloric spasm, beginning pyloric stenosis and other less common and even less well-defined conditions thrust ourselves forward in turn for consideration. For although the diagnosis in the classical case is simple, in many others we grope for weeks, and even when all is over we do not feel confident that we have solved the nature of the disturbance. In cases of this description the duodenal catheter, and at times the soft rubber ball-tube as well, has been of assistance. To cite an instance:

E. K., aged five weeks, weight $7\frac{3}{4}$ pounds, getting $\frac{1}{2}$ milk, $\frac{1}{2}$ water, 4 ounces every three hours. History of increasing propulsive vomiting for past week. When two and one-half weeks of age weighed 8 pounds 13 ounces.

March 5. Fed two hours ago. Gastric area prominent. Marked peristaltic waves from left to right, rarely crossing median line, marked double wave and hour-glass formation. Baby seemed uneasy; 14 (F.) catheter passed; 5 c.c. acid congo negative milk obtained. When stomach was

emptied peristalsis ceased, although distention persisted. Catheter passed again. Duodenum easily entered. Bile obtained.

March 6. Observed two hours after feeding again. Given 1 ounce of water, and visible peristalsis and hour-glass contraction of stomach began, followed by vomiting of water; 15 (F.) passed, some cardiospasm, or esophagospasm. Duodenum readily entered. No visible peristalsis while catheter was in esophagus, stomach, or duodenum. Some large casein masses in stool.

March 8. Same gastric signs as previously noted. Catheter again passed and bile obtained. Still vomiting.

March 10. Gastric peristalsis and hour-glass formation less.

March 17. Not vomiting any more. Still has gastric peristaltic wave and tumor formation. Child is restless and squirms a great deal.

This case has been selected for illustration because in spite of marked visible gastric peristalsis and tumor formation, frequently assuming the typical hour-glass shape, a 15 (F.) catheter was passed through the pylorus into the duodenum. We have record of a similar case which was demonstrated to students as a typical case of pyloric stenosis, on account of these motor phenomena, where the catheter was readily inserted into the duodenum and duodenal feeding successfully carried out in the auditorium.

If we merely fail to enter the duodenum we should certainly err to attribute this failure to spasm or stenosis. But if we are certain of our technique and meet with a case offering persistent obstruction at the level of the pylorus we are justified in attributing this hindrance and the symptoms to pyloric obstruction. It is in such a case in which the catheter is repulsed again and again at the same level, where we finally feel the resistance yield and the catheter pass that we diagnosticate spasm. We may use the *x*-ray to confirm our belief that the duodenum has been entered. However, if we are absolutely unable to enter the intestine after repeated attempts in the case of an infant showing symptoms of pyloric spasm or stenosis, the latter must be regarded as the more likely pathologic condition.

There are some excellent clinicians who do not believe in pylorospasm unassociated with a stenosis, and others who hold to a dualistic theory, dividing the cases into those of simple spasm and others of organic stenosis, which may be accompanied by

spasm. The difficulty has been twofold, to prove the existence of spasm during life, and to differentiate post mortem between stenosis and systolic contraction of the pylorus. The catheter is of great service in this regard, as it furnishes a standard of measurement *in vivo* of the pylorus. To obtain a clearer insight into this pathologic condition we must have a standard by which stenosis can be judged; the most trustworthy is one which can be applied during life. We suggest that the 15 (F.) catheter be used for this purpose in infants; if this catheter having a diameter of almost 5 mm. can be passed through the pylorus of an infant the clinical diagnosis of organic stenosis is not warranted. Using this standard we are able to state definitely, from our experience, that pylorospasm may be present without stenosis. For what other conconclusion is to be drawn from cases characterized by persistent vomiting, marked gastric peristaltic wave, visible gastric tumor with hour-glass formation, in which obstruction is overcome by the catheter and the duodenum entered. As we have observed, we have tested several cases of this description, some diagnosticated as pyloric stenosis but which were evidently spastic in nature.

Associated with pylorospasm we encountered very often a spasm of the cardia (Ibrahim). This was frequently so marked that the food did not enter the stomach. Furthermore, we found a spasm of the pharynx (Finkelstein) and possibly of the esophagus, indeed, a general nervous disturbance, which taken in conjunction with the secretory phenomena about to be described, may well be grouped into a symptom complex, and designated by a name such as "vagatonie." However, this broader phase of the subject must be left to a future time. The anomaly of secretion which we refer to has not to our knowledge been previously described. For some time it has been recognized that gastric hypersecretion is a symptom of many cases of pylorospasm or stenosis. We found duodenal hypersecretion or succorrhea frequently associated with this gastric hypersecretion. This duodenal juice was alkaline, and contained the three pancreatic ferments to a considerable degree, so that the condition may be termed "pancreatic hypersecretion or succorrhea." It would seem, moreover, that just as there are cases of pyloro-

spasm not associated with gastric hypersecretion, so there are cases unassociated with pancreatic hypersection.

Use of Catheter for Therapy. Infants suffering from pylorospasm or pyloric stenosis frequently die of inanition. In several cases of this nature the usual mixtures of milk have been introduced by means of the catheter directly into the duodenum. This has been carried out for various pathologic conditions in adults, more expecially by Einhorn,[1] and by Gross. It is unnecessary to enter into a description of the indications or of the technique of this procedure. It should be reserved for such cases as do not retain food by gavage; the food should be given slowly and in not too large amounts. Following duodenal feeding there has been a gain in weight, a disappearance of subnormal temperature, and relaxation of spasm. The mere passage of the catheter seems to relieve the spastic condition.

The Study of the Pancreatic Ferments. In addition to these practical applications in diagnosis and treatment, the catheter affords an opportunity of pursuing interesting physiologic studies. It is possible to obtain pancreatic juice, in a way similar to that in which we obtain gastric juice, and to make a study of this fluid directly, instead of depending upon an examination of the feces during life or of extracts of the pancreas after death. Tests carried out by this means show that the pancreatic ferments are found in the duodenum soon after birth, even before the infant has nursed. The amylase is small in amount at first, but increases decidedly during the first weeks of life. It is difficult to understand why amylase should be secreted, why the newborn nursing baby should be provided with a starch-splitting ferment. However, it shows in a conclusive manner that the clinical deduction of Jacobi[2] and of Heubner,[3] that infants can digest starchy food even during the first few months of life, is borne out by physiologic investigation. The secretion of amylase by a nursing baby must be intercepted as an argument against absolute specificity in the elaboration of ferments by the pancreas.

As may be imagined the clinical field is large to which these

[1] M. Einhorn, Med. Record, January, 1910.
[2] A. Jacobi, Gerhardt's Handbuch, 1876.
[3] O. Heubner, Berl. klin. Woch., 1895, No. 10

ferment examinations may be applied. An examination of marasmus cases proved that this nutritional disturbance cannot be attributed to a lack of pancreatic ferments, as had been suggested at various times. It showed also that in these cases there is at times a marked hypersection of duodenal juice, a succorrhea entirely unaccompanied by gastric hypersecretion. This juice is thin, watery, very profuse, and contains the three pancreatic ferments, although lipase in diminished amount. This pancreatic hypersecretion we have termed "paralytic succorrhea" as it seemed analogous to the hypersecretion of the parotid gland which Claude Bernard produced by division of the chorda tympani nerve. It is in marked contrast to the pancreatic hypersecretion described above in connection with cases of pylorospasm, for in the cases of spasm we find in addition a gastric hypersecretion; the pancreatic juice is probably stimulated by its normal agent the gastric juice. Such cases may be termed "functional pancreatic hypersecretion," and may later develop into the paralytic type.

Icterus Neonatorum. Other investigations have been carried out by this method, and still more lend themselves to its application. By means of the catheter the excretion of bile in the newborn was studied, and its relation to icterus neonatorum. Among other things it was found that this jaundice precedes the excretion of bile into the intestine; that bile is very rarely excreted during the first twelve hours of life and to a variable extent during the subsequent twenty-four hours; that when jaundice is marked, bile is present in the duodenum in increased amount. In the newborn infants a No. 14 (F.) catheter was employed, and difficulty in its use was rarely experienced.

Congenital Obliteration of the Bile Ducts. A study of a case of congenital obliteration of the bile ducts suggested the advisability of subdividing these cases into two groups according to whether or not the pancreatic juice enters the duodenum. In one group the pancreatic duct is obstructed together with the bile duct at the papilla of Vater, but is compensated for by the presence of an accessory duct of Santorini; this may be called the "compensated" form. In the other no accessory duct exists, and pancreatic juice does not reach the intestine; this is the rarer form and may be termed the "uncompensated" variety.

Bacteriologic Duodenal Examination. Without entering into a discussion of its merits we may add that the catheter may be applied as a method for diagnosis and study of the bacterial flora of the intestine. For this purpose we protect the tip by means of a sterilized gelatin capsule which is not dissolved for some minutes, not until the pylorus is passed. In this way a study of the influence of various factors upon the bacterial flora can be pursued. In a case of typhoid fever the typhoid bacillus was aspirated from the duodenum of a twenty-two-months-old infant, which suggests a possible application of this method. It is possible that this technique may be also of value in connection with diseases of known or unknown origin associated with animal parasites, for instance in amebic infection of the intestine or liver. It would seem to have usefulness in the study of enteritis and of dysentery, which it is difficult to investigate satisfactorily by the aid of cultures from the stool, on account of the vast number of contaminating bacteria. This difficulty is not encountered in cultures taken from the upper part of the intestinal tract.

Summary. It is readily possible to pass a simple Nélaton catheter 15 (F.) through the stomach and into the duodenum in infants from the earliest period up to the age of about two years. Such an "infant duodenal catheter" may be used to differentiate between spasm and stenosis of the pylorus, making use of the *x*-ray if necessary to prove that the catheter has reached the duodenum, and that there is no organic obstruction at the pyloric sphincter. In these cases, and in others similar, this catheter has been used for duodenal feeding, as has been carried out in adults by means of duodenal tubes.

In addition to these practical uses the catheter offers an opportunity to study the interesting motor phenomena frequently associated with pyloric obstruction. It was found that marked visible peristalsis and pseudo-tumor formation of the stomach may exist, and the pylorus nevertheless may admit the passage of this catheter, showing that no organic obstruction at this point existed, and that these signs are not diagnostic of hypertrophic stenosis.

A direct study of the ferments of the pancreas is possible by this means, which has decided advantages over the previous

indirect methods, namely, tests of the stool during life, or of pancreatic extracts after death. It was found in this way that the three ferments, including the starch-splitting ferment, are secreted in earliest infancy. A study of marasmus from this point of view showed that this condition is not associated with nor, as has been suggested, is it the result of a marked decrease in the pancreatic ferments. Indeed, some of the atrophic infants, although secreting little gastric juice to act as a stimulus, secreted a very large amount of thin, watery juice containing all the pancreatic ferments, although weak in lipase. This pathologic condition we have termed "paralytic hypersecretion or succorrhea," as it suggested the hypersecretion following the severing of the chorda tympani nerve.

Cases of pylorospasm associated with gastric hypersecretion furnished numerous examples of pancreatic overactivity of a quite different nature. In these instances the gland probably was overstimulated by the normal agent, the gastric juice. Such cases may be termed "functional pancreatic hypersecretion," and later may develop into the paralytic type.

The catheter offered an opportunity for the study of icterus neonatorum from a new point of view, of ascertaining when the bile is first excreted into the duodenum in the newborn, and its relation to jaundice. It was used also in a case of congenital obliteration of the bile ducts in order to test for the presence of pancreatic ferments. In instances of this disease it may be employed in this way to distinguish clinically the cases where the pancreatic juices are excreted into the intestine, from those where this excretion as well as that of the liver is absolutely obstructed.

A study of the bacteria of the duodenum in infants was made. It is suggested that the catheter armed with a sterile gelatin capsule might be used in this way to investigate such infections as enteritis, or dysentery, or even those due to animal parasites; for example, ameba, or others of unknown origin. In a case of typhoid fever in an infant, typhoid bacilli were isolated in almost pure culture from the duodenal fluid.

There are certainly other subjects in the fields of clinical and experimental medicine where the infant duodenal catheter may be used to advantage.

A CLINICAL STUDY OF A THOUSAND CASES OF ULCER OF THE STOMACH AND DUODENUM

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In the study of the thousand cases of ulcer of the stomach and duodenum, great care has been exercised to eliminate all cases in which there has been the slightest question as to the diagnosis and suspected cases in which the diagnosis has been the least doubtful, have been excluded from this report. The thousand cases occurred in 12,598 patients effected with various gastric disturbances (7.8 per cent.).

Age. As is observed in the following table the largest proportion of cases occur between the twentieth and fiftieth years and the greatest number between the twentieth and thirtieth years.

Age.	Cases.	Per cent.
0 to 10	2	0.20
10 to 20	162	16.20
20 to 30	345	34.50
30 to 40	229	22.90
40 to 50	128	12.50
50 to 60	93	9.30
60 to 70	38	3.80
Over 70	3	0.30
	1000	

Sex. Of the total number of cases there are 676 males and 324 females. The following table illustrates the number of cases observed in males and females according to age.

Years.	Males.	Females.	Total.
0 to 10	2	0	2
10 to 20	124	38	162
20 to 30	262	83	345
30 to 40	119	110	229
40 to 50	91	37	128
50 to 60	48	45	93
60 to 70	29	9	38
Over 70	1	2	3

Of the thousand cases, 31 were found in cooks, 18 in workers in metals, 12 in workers in porcelain, 8 were miners, 28 were tailors, 15 were shoemakers, and 19 were blacksmiths.

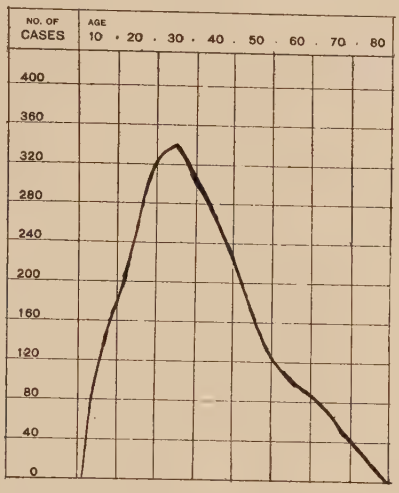

Fig. 1.—Age diagram of 1000 cases of ulcer.

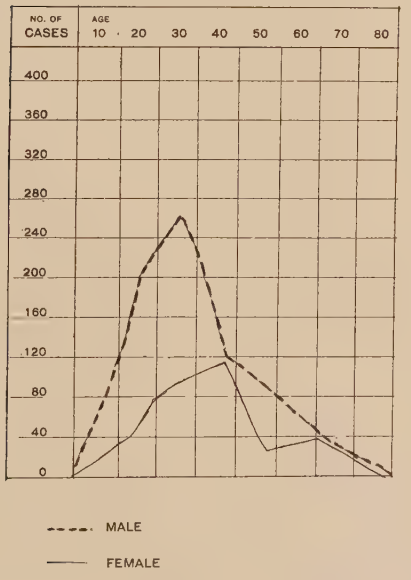

Fig. 2.—Sex and age diagram of 1000 cases of ulcer.

A definite history of trauma was elicited in 23 cases, in 10 of which there had been blows on the abdomen.

Anemia. In 324 of our cases in which hemoglobin estimations had been recorded, anemia was present in 211 cases (65 per cent.). The average of the hemoglobin estimations was 61 per cent.; this does not, however, include those cases accompanied by severe hemorrhages. In 302 cases in which hematemesis or melena occurred, the average hemoglobin estimation was 46 per cent.

Cardiac and Vascular Changes. Chronic endocarditis was present in 43 cases (4.3 per cent.); arteriosclerosis in 153 (15.3 per cent.).

Previous Disorders of Digestion. In the 1000 cases there was a history of some previous digestive disturbance in 482 cases (48.2 per cent.). Some of these disturbances must have been premonitory symptoms of the ulcer itself, inasmuch as there is often great difficulty in distinguishing early signs of ulcer from ordinary slight gastric disturbances.

Excesses in Food and Drink. The history of former indiscretions in diet was obtained in 433 instances (43.3 per cent.); but only in 129 (12.9 per cent.) did the patient attribute his disease to some specific error in diet.

A history of alcoholism was obtained in 214 instances (21.4 per cent.).

Infectious Diseases. A history of syphilis was obtained in 52 instances, yet only in 5 could the ulcer be directly attributed to this disease. Tuberculosis of the lungs was present in 26 instances, but as far as could be observed this disease appeared to have no etiological bearing upon the production of the ulcer.

The Gastric Secretion in Ulcer. Of the thousand cases the gastric secretion was examined in 810 instances.

	Cases.	Per cent.
Normal acidity was observed in	376	46.4
Hyperchlorhydria was observed in	246	30.3
Hypochlorhydria and anacidity	188	23.2
	810	

Of the 810 cases, consisting of 516 males and 294 females, the acidities were as follows:

	Males.		Females.	
	Cases.	Per cent.	Cases.	Per cent.
Normal acidity	271	33.5	105	12.9
Hyperchlorhydria	161	19.8	85	10.5
Hypochlorhydria and anacidity	84	10.4	104	12.8
	516		294	

Hyperacidity was proportionately more frequently observed in males and subacidity in females, while the greatest number of males as well as females presented a normal acidity. It is interesting to note the relation of acidities to the duration of the disease. In acute ulcers, and especially those accompanied by recent hemorrhages, the acidity is very high, while in chronic forms the acidity is low. In 128 cases of acute ulcer, of which 75 were males and 53 were females, 96 (61 males and 35 females) presented high acidities.

	Males.		Females.	
	Cases.	Per cent.	Cases.	Per cent.
Normal acidity	12	9.3	8	0.6
Hyperchlorhydria	61	47.6	35	27.3
Hypochlorhydria	2	1.6	10	7.7
	75		53	

Of the 426 cases of chronic ulcers of long duration the tendency is toward low acidities. The following table illustrates this condition:

	Males.		Females.	
	Cases.	Per cent.	Cases.	Per cent.
Normal acidity	94	22.0	85	19.9
Hyperchlorhydria	35	8.3	39	9.1
Hypochlorhydria	80	18.6	93	21.8
Total	209	48.9	217	50.8

Duration of Symptoms. The average duration of symptoms in ulcer is twelve years. The following table illustrates the average duration of symptoms in males and females according to age.

Age.	Males.	Average duration of symptoms in years.	Females.	Average duration of symptoms in years.
0 to 10	2	½	0	
10 to 20	124	2	38	1½
20 to 30	262	11	83	10½
30 to 40	119	19	119	13½
40 to 50	91	14	37	16
50 to 60	48	16½	45	19
60 to 70	29	17	9	19½
Over 70	1	20	2	12
	676		333	

PAIN. Pain, the most prominent feature of ulcer, was present in 94 per cent. of our cases. It is most prominent in those cases accompanied by hyperchlorhydria. Of the 810 cases in which the gastric contents were analyzed the relation of pain to acidity is presented in the following table, from which it is evident that pain is most pronounced in those instances associated with high acidity:

		Absent.		Moderate.		Moderately severe.		Severe.	
	Cases.	No.	%	No.	%	No.	%	No.	%
Normal acidity . . .	376	2	0.2	92	11.3	123	15.1	159	19.6
Hyperchlorhydria . . .	246	1	0.1	8	9.0	35	4.3	202	24.9
Hypochlorhydria . . .	188	7	0.7	59	7.3	82	10.1	40	5.0
	810			159		240		401	

TIME OF APPEARANCE OF PAIN. Of the 1000 cases the pain appeared within the first hour after meals in 223 instances, between one and two hours in 188, after two hours in 491, and in 38 it appeared irregularly.

EFFECT OF FOOD UPON PAIN. The pain was aggravated in 212 instances by the ingestion of food and was relieved in 619 instances by the taking of food. In 109 instances the pain was neither increased nor relieved by the taking of food.

INTERMISSIONS OF PAIN. In 563 instances of the 940 cases in which pain was present there were one or more periods in which distinct intermissions of pain occurred varying from one to twelve months or more. The following table presents these according to periods of intermission in months.

Cases.	Months of intermission.
94	1 to 2
72	2 to 3
82	3 to 4
79	4 to 5
48	5 to 6
26	6 to 7
38	7 to 8
34	8 to 9
17	9 to 10
20	10 to 11
31	11 to 12
22	12 or more.
563	

TENDERNESS. Of the 1000 cases epigastric tenderness was present in 908 cases (90.8 per cent.). A tender area was noted to

the right of the median line in 41 cases (4.1 per cent.). The dorsal, together with an epigastric tender spot, was noted in 523 instances (52.3 per cent.). A dorsal area alone in 25 (2.5 per cent.). No tender area in 26 instances (2.6 per cent.).

Vomiting. Vomiting is another very prominent symptom, though not as constant as the pain. It occurred in 676 of our cases (67.6 per cent.). It is proportionately more frequent in those instances in which pain appears early. Of the 940 cases in which pain was present there were 223 having pain within the first hour, of which 194 had vomiting. There were 188 with pain between the first and second hours, of which 143 had vomiting; 529 manifested pain two hours after meals (or pain appeared irregularly), of which 324 had vomiting. The following table illustrates this condition.

Time of appearance of pain in hours.	Cases with pain.	Cases with vomiting.	General per cent.	Per cent. of cases of vomiting in proportion to the cases with pain.
In one hour	223	194	29.3	87.0
In one to two hours . . .	188	143	21.6	76.6
After two hours or irregularly .	529	324	49.0	61.2
Total	940	661		

Of the 40 cases of ulcer not accompanied by pain, vomiting occurred in 16 cases (40 per cent.).

Vomiting and Acidity. Of the 810 cases in which an examination was made of the gastric contents, the relation of the vomiting to the acidity is illustrated in the accompanying table. There were 676 of these cases in which vomiting was present. Of these there were 531 in which analyses were made. Vomiting is definitely more prominent in those instances accompanied by high acidity.

		Moderate vomiting.		Severe vomiting.	
Acidity.	Cases.	Number.	Per cent.	Number.	Per cent.
Normal acidity . . .	296	125	23.5	171	32.5
Hyperchlorhydria . .	140	18	3.3	122	22.8
Hypochlorhydria . .	95	76	14.3	19	3.5

Hematemesis. Gastric hemorrhage was manifested or a history of this symptom was presented in 228 of the 1000 cases, that is in 22.8 per cent. In the following table the proportion of cases accompanied by a single hemorrhage or with multiple hemorrhages are presented according to age.

Years.	Cases with hemorrhage.	Per cent. of cases with hemorrhage.	Proportion cases single hemorrhage. Number.	Per cent.	Proportion cases multiple hemorrhage. Number.	Per cent.
0 to 10	0	0.0	0	0.0	0	0.0
10 to 20	48	21.0	17	7.4	31	13.6
20 to 30	81	35.5	23	10.0	58	25.4
30 to 40	42	18.3	28	12.7	13	5.7
40 to 50	29	12.8	8	3.4	21	9.0
50 to 60	20	8.8	6	2.6	14	6.0
60 to 70	8	3.5	6	2.6	2	0.9
Over 70	0	0.0	0	0.0	0	
Total	228	99.6	88	38.7	139	60.6

Melena. Tar-colored stools or a history of this condition was presented in 515 of the 1000 cases, that is 51.5 per cent. The following table illustrates the number and percentage of these cases at various ages; the largest proportion appearing between the tenth and thirtieth years.

Years:	Cases with melena.	Per cent. of cases with melena.
0 to 10	0	0.0
10 to 20	103	10.3
20 to 30	161	16.1
30 to 40	98	9.8
40 to 50	66	6.6
50 to 60	61	6.1
60 to 70	24	2.4
Over 70	2	0.2
	515	51.5

It is also interesting to note the proportion of cases with melena, and compare this condition with hematemesis observed at various ages, as is illustrated in the accompanying table. Melena is over twice as frequent as gastric hemorrhage, and occurs much more frequently after the fortieth year of age than is observed with hematemesis.

Comparison of Cases with Hematemesis and Melena at Various Ages.

Ages.	Gastric hemorrhage. Cases.	Per cent.	Melena. Cases.	Per cent.
0 to 10	0	0.0	0	0.0
10 to 20	48	4.8	103	10.3
20 to 30	81	8.1	161	16.1
30 to 40	42	4.2	98	9.8
40 to 50	29	2.9	66	6.6
50 to 60	20	2.0	61	6.1
60 to 70	8	0.8	24	2.4
Over 70	0	0.0	2	0.2
	228		515	

There were 287 cases accompanied by melena without any evidence of hematemesis. These cases are presented according to age in the following table. They are cases of duodenal ulcers which are to be presented later on.

Age.	Case.	Per cent.
10 to 20	55	19.5
20 to 30	82	28.3
30 to 40	56	19.5
40 to 50	37	12.9
50 to 60	41	14.2
60 to 70	16	5.5
Over 70	0	0.0
	287	

Occult Blood. The test for occult blood was made constantly only with feces. The stools were examined in 539 cases of the 1000 cases. Of these 467 gave one or more positive results (86.6 per cent.). The examinations here noted were only made in those instances in which visible blood was absent, or had not appeared for a considerable length of time before the test had been made. Blood was not always present in the first test but frequently appeared sometime during the course of the disorder.

Einhorn String Test. The string test was made in 41 of our cases and was found positive in 34 (83 per cent.). The results obtained by means of this test are about as sensitive as the test for occult blood.

Complications. Atony of the stomach was noted in 321 (32.1 per cent.) of our cases and enteroptosis was noted in 411 instances (41.1 per cent.). Evidences of dilatation of the stomach were observed in 336 instances (38.4 per cent.). A tumor was palpable in the form of an hypertrophied pylorus in 25 of our cases (2.5 per cent.), and perforation occurred in ten cases (1 per cent.).

Duodenal Ulcers. Of the 1000 cases of ulcer 529 were duodenal, (52.9 per cent.), 409 gastric (40.9 per cent.), and 62 (6.2 per cent.) undetermined. The largest number of duodenal ulcers occurred between the twentieth and thirtieth years. The following table illustrates the number of cases of duodenal ulcer arranged according to age:

Years.	Cases.	Per cent.
10 to 20	55	10.3
20 to 30	159	30.0
30 to 40	149	28.2
40 to 50	91	17.2
50 to 60	43	8.2
60 to 70	32	6.0
Over 70	0	0.0
	529	

Sex. The largest proportion of cases occurred in males, *i. e.*, 307 males (58 per cent.) and 222 females (42 per cent.). The following table indicates the number of males and females at various ages.

	Males.		Females.	
Years.	No.	Per cent.	No.	Per cent.
10 to 20	31	5.8	24	4.5
20 to 30	85	16.1	74	13.9
30 to 40	87	16.4	62	11.7
40 to 50	66	12.4	25	4.7
50 to 60	11	2.0	32	6.0
60 to 70	27	5.1	5	0.9
	307		222	

Acidity. Of the 529 cases the secretion was analyzed in 402. Of the 402 there were 195 with normal acidity, 142 with hyperchlorhydria and 65 with hypochlorhydria. The accompanying table illustrates this condition:

	No.	Per cent.
Normal acidity	195	48.5
Hyperchlorhydria	142	35.3
Hypochlorhydria	65	16.1
	402	

Of the 402 cases there were 213 males and 189 females which are arranged according to their acidities in the following table. Hyperacidity being more frequently observed in males and subacidity in females.

	Male.		Female.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Normal acidity	120	29.7	75	18.6	195	48.3
Hyperchlorhydria	79	19.6	63	15.6	142	35.2
Hypochlorhydria	14	3.4	51	12.4	65	18.8
	213		189		402	

Pain. Pain was present in 512 of our duodenal cases, (96.5 per cent.). It was absent in 17 cases. It was most prominent in

those cases with hyperacidity. Of the 402 cases in which the gastric contents were examined, the relation of the pain to the acidity is illustrated in the following table, the pain being more severe in those instances associated with high acidity:

		Absent.		Mild.		Moderately severe.		Severe.	
	Cases.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Normal acidity	195	1	0.2	45	12.1	59	14.6	90	22.1
Hyperchlorhydria	142	1	0.2	6	1.4	24	5.9	111	27.3
Hypochlorhydria	65	5	1.2	25	6.2	10	2.4	25	6.2
	402			76		93		226	

Intermissions of Pain. Of the 512 cases in which pain was present, 316 presented records showing distinct periods in which the pain had disappeared for a time; one month to twelve months or more, (63 per cent.). The following table illustrates the number of cases presenting the intermissions of pain according to the number of months.

Cases.	Intermissions in pain in months.
53	1 to 2
36	2 to 3
44	3 to 4
37	4 to 5
34	5 to 6
17	6 to 7
23	7 to 8
29	8 to 9
9	9 to 10
15	10 to 11
14	11 to 12
5	12 or more.
316	

Tenderness. Of the 529 cases epigastric tenderness was present in 474 cases (89.4 per cent.). A tender area to the right or left of the median line in 41 cases (7.7 per cent.). A dorsal tender area together with an epigastric spot was present in 289 cases (54.6 per cent.), and a dorsal tender area alone in 6 cases (1.1 per cent.); no tender area in 8 cases (1.5 per cent.).

Vomiting. Vomiting occurred in 113 of our duodenal ulcers, that is 21 per cent.

Vomiting and Acidity. Of the 402 cases in which the gastric contents was analyzed the relation of the acidity to vomiting is as illustrated in the following table. There were 113 cases in which

vomiting occurred, of which the gastric contents were examined in 92. It is here demonstrated that vomiting is more frequent in those cases accompanied by high acidity.

	No.	Moderate vomiting.		Severe vomiting.	
Normal acidity	48	20	4.8	28	30.4
Hyperchlorhydria	38	6	6.5	32	34.8
Hypochlorhydria	6	5	5.4	1	1.0
	92			61	

Melena. Tar-colored stools or a history of this condition appeared in 287 of our 529 cases, (54 per cent.). The following table presents the number of cases according to age:

Age.	Cases.	Per cent.
10 to 20	55	19.5
20 to 30	82	28.3
30 to 40	56	19.5
40 to 50	37	12.9
50 to 60	41	14.2
60 to 70	16	5.5
	287	

Occult Blood. Of the 529 cases, an examination of the feces was made in 381. Of this number, 315 presented one or more positive tests for occult blood (83 per cent.). The examinations here noted include those cases alone in which visible blood was entirely absent, or had not been present for a considerable length of time before the test for occult blood was made. The blood was frequently absent in the first examination, but usually appeared sometime during the course of the disorder, and especially when the symptoms became aggravated. It gradually disappeared as recovery took place.

Results of Treatment of Gastric and Duodenal Ulcers. Of the 1000 cases, 885 were under direct observation during the entire course of treatment. In the remaining 115 the diagnosis was simply made, treatment was not instituted, or if so, was only imperfectly carried out.

Of the 885 cases, 794 were treated medically and 91 surgically. Of the 794 treated medically, 20 were required to seek surgical aid later on account of the failure of medical treatment. Of the 794 treated medically, 521 undertook the rest cure treatment, while 273 were treated as ambulatory patients.

Of the 521 treated by the rest cure, 404 had the Leube treatment, and 117 the Lenhartz treatment, or a slight modification of the same. Of the 404 treated by the Leube, 291 (72 per cent.) were cured, 97 (24 per cent.) were not cured, and 16 (4 per cent.) died. Of the 117 treated by the Lenhartz treatment, 78 (66 per cent.) were cured, 34 (29 per cent.) were not cured, and 5 (5 per cent.) died.

Of the 273 cases treated as ambulatory patients, 153 were treated with nitrate of silver, 110 with subnitrate of bismuth, and 10 by the olive oil method. Of the 153 treated with the nitrate of silver, 73 (47 per cent.) were cured, while 80 (53 per cent.) were not cured. Of the 110 treated with subnitrate of bismuth, 56 (50 per cent.) were cured, while 54 (49 per cent.) were not cured. Of the 10 treated by the olive oil method, 4 (40 per cent.) were cured while 6 (60 per cent.) were not cured. The following table illustrates the percentage of recovery by various methods of treatment:

		Cured.		Not cured.		Died.	
No.	Form of treatment.	No.	Per cent.	No.	Per cent.	No.	Per cent.
404	Leube	291	72	97	24	16	4
117	Lenhartz	78	66	34	29	5	5
153	Nitrate of silver . . .	73	47	80	53	Ambulatory cases.	
110	Subnitrate of bismuth .	56	50	54	49	Ambulatory cases.	
10	Olive oil	4	40	6	60	Ambulatory cases.	

End Results. Of the 291 cases treated by the Leube method and cured, 83 could be followed for a period of five years or longer after the treatment. Of these 62 (74 per cent.) remained permanently well, and 21 (25 per cent.) had relapses.

Of the 78 treated by the Lenhartz treatment and cured, 45 could be followed for a period of five years or longer after the treatment. Of these, 35 (77 per cent.) remained permanently well, while 10 (22 per cent.) had relapses.

Results of Surgical Treatment. Of the 91 cases operated on, 64 (71 per cent.) were cured, 20 (22 per cent.) were not cured, and 7 (70 per cent.) died. Of these 10 had perforations, of which 6 (60 per cent.) recovered, while 4 (40 per cent.) died.

End Results. Of the 64 cases operated on and cured, 45 could be followed for a period of five years or longer after treatment. Of these 41 (91 per cent.) remained permanently well, and 4 (9 per cent.) had relapses.

Einhorn Duodenal Feeding. A few cases of ulcer which did not yield to the usual treatment were treated by Einhorn's duodenal method of feeding. While the results seemed satisfactory, the number of cases were too few to be incorporated in this report.

Conclusions. From a careful study of the 1000 cases of ulcers of the stomach and duodenum the following conclusions may be safely drawn.

1. In patients suffering from various gastric disturbances, 7.8 per cent. are affected with ulcers.

2. The largest proportion of ulcers occur between the twentieth and fiftieth year of age.

3. More than twice as many males are affected as females.

4. Anemia is present in a large proportion of the cases of ulcer.

5. A history of the overindulgence in food or drink can be obtained in almost half of the number of cases of ulcer.

6. The greatest proportion of cases of ulcer presents a normal acidity, *i. e.*, 46 per cent.; 30 per cent. a hyperacidity, and 23 per cent. a subacidity. Hyperacidity is proportionately more frequently observed in males and subacidity in females. In recent ulcers and especially those accompanied by recent hemorrhage, the acidity is very high, while in chronic forms the acidity is low.

7. The average duration of symptoms is twelve years.

8. The most prominent symptom of ulcer (pain) occurs in 94 per cent. of cases, and pain is most frequent in cases associated with a high acidity. Pain appears sometimes immediately after the taking of food (gastric ulcer), and at times long after the taking of food (duodenal ulcer). In many instances there are one or more periods of intermission of pain as well as the other symptoms; these periods vary from one to many months.

9. An epigastric tender area is present in at least 90 per cent. of all cases, a dorsal tender area in 32 per cent.

10. Vomiting is a very prominent symptom occurring in 67 per cent. of cases.

11. Hematemesis is present in 22 per cent. of cases and melena in 51 per cent. Melena is more than twice as frequent a gastric hemorrhage. Occult blood is present in 81 per cent. of the cases.

12. Of the 1000 cases of ulcer, 52 per cent. are duodenal and 40 per cent. gastric; the largest proportion occurring in males, (58 per cent.).

13. Of the duodenal ulcers, 48 per cent. present normal acidity, 35 per cent. hyperacidity, and 16 per cent. a subacidity, hyperacidity being more frequently observed in males and subacidity in females.

14. Pain is present in 96.5 per cent. of duodenal ulcers, and is most prominent in cases with hyperacidity.

15. Distinct periods of intermission from pain and other symptoms, varying from one to twelve months or more are exceedingly common in this affection.

16. Epigastric tenderness is present in 89 per cent. of the duodenal cases; a tender area to the right or left of the median line in 7 per cent.

17. Vomiting occurs in 21 per cent. of duodenal cases, and is more frequent in those accompanied by high acidity.

18. Melena occurs in 54 per cent. of duodenal cases, and occult blood is found in the stools in 83 per cent.

19. Seventy-two per cent. of cases of peptic ulcers treated by the Leube treatment are cured, 66 per cent. by the Lenhartz, 47 per cent. by the ambulatory treatment administering nitrate of silver, 50 per cent. with subnitrate of bismuth, and 40 per cent. with olive oil. Of the cases treated by the Leube cure, 74 per cent. remained permanently well, while 77 per cent. of those treated by the Lenhartz cure, likewise remained permanently well.

20. 71 per cent. of the cases operated on are cured, 91 per cent. remaining permanently well.

The diagnosis of ulcer is often most difficult. The diagnosis of typical cases is not difficult, but the atypical forms form a great proportion of cases, and great difficulty is often experienced in drawing conclusions concerning such cases. Some of the important symptoms, such as pain and epigastric tenderness, as well as nausea, vomiting, hematemesis, and melena, may be absent, or may be so overshadowed by other symptoms as to become insignificant.

The diagnosis of ulcer should never be made without the detection

of occult blood in the stools, and yet when it is remembered that occult blood may appear in many other conditions, and that even in ulcer it often disappears, especially when the ulcer is healing, the difficulties in diagnosis become even greater.

The diagnosis between duodenal and gastric ulcer is often very difficult and many clinicians consider it is impossible in many instances to differentiate between the two. It is generally admitted that pain appearing two hours or more after meals (hunger pains) is indicative of ulcer of the duodenum, while pain appearing early is gastric. Hemorrhage is mainly observed in the vomitus in gastric ulcer, and most frequently in the feces in duodenal ulcer; but is very often observed in both in either condition, and is of but slight importance in distinguishing the two forms without blood, is persistently observed in the feces without being present in the gastric secretion.

Peptic ulcers are frequently mistaken for gastric neuroses associated with hyperacidity, and it is of the greatest importance to distinguish between these conditions.

Gall-bladder disturbances are to be differentiated from duodenal ulcers, but the diagnosis between the two conditions are often very difficult and sometimes impossible.

There can be no question but that a large proportion of ulcer cases recover under medical treatment. According to our observations, 72 per cent. by the Leube cure, 66 per cent. by the Lenhartz cure; this is in comparison to 71 per cent. treated surgically. When an ulcer patient is treated medically he should be thoroughly treated, and ambulatory treatment should never be instituted. As we have shown, the results of ambulatory treatment are exceedingly unsatisfactory, inasmuch as in but from 40 to 50 per cent. of cases so treated is a cure effected. I believe that many ulcer cases do not recover because the treatment is not sufficiently prolonged. A rest cure of but a few weeks is often insufficient. In severe cases the patient should be put to bed for six or eight or even more weeks. The answer to the question whether the Leube or the Lenhartz treatment should be undertaken, depends largely upon the patient and the severity of the symptoms. Quite satisfactory results are often obtained by the Leube cure, and at times

on account of the persistent nausea, vomiting, and pain one is forced to follow this form of treatment. It is best when possible, however, to institute the Lenhartz treatment, for a restriction to liquid food is often unnecessary and usually results in great weakness and exhaustion. The anemia too frequently found accompanying this condition is often very extreme and the small quantities of milk which are consumed cannot prevent the onset of rapid exhaustion and emaciation.

Surgical intervention should only be considered if medical treatment has been persisted in for a sufficiently long period of time, and had not been found effectual; especially is it indicated in those cases accompanied by severe and persistent pain, vomiting, or hemorrhage, or in ulcers recurring notwithstanding thorough medical cure. The operation is indicated too in all pyloric or duodenal ulcers accompanied by stenosis. In ulcers situated at other parts of the stomach, operation gives but slight relief unless radical procedures (resection or excision) are undertaken. Operation should be promptly practised in all cases of perforation.

DISCUSSION

Dr. W. T. Howard: I should like to ask Dr. Friedenwald if he has followed any of his cases of gastric ulcer long enough to note whether they developed carcinoma. We tried to follow this out, and 4 of 82 cases of gastric ulcer developed signs of carcinomatosis. Another point in that small series, we found that hyperacidity was not present, but low acidosis.

Dr. W. S. Thayer: I merely wish to emphasize the importance of what Dr. Friedenwald has said in regard to the advisability of long treatment in bed, especially in the case of young individuals with gastric ulcer. A thorough rest treatment, beginning often with long-continued rectal feeding, followed by a very gradually increasing diet, is, it seems to me, the main essential of treatment of outspoken gastric ulcer in the young.

Dr. J. M. Anders: I would like to ask Dr. Friedenwald whether he distinguished between acute ulcer of the stomach and chronic ulcer with

tumor, and if so, whether he obtained the same result in the former as he did in the latter?

Dr. Friedenwald: I have observed many cases of gastric cancer, and in but a small proportion of cases could the cancer be observed to have been formed on the base of an old ulcer. The acute ulcers do better under medical treatment, the chronic forms sometimes do well under this form of treatment, and if they do not, they should be operated upon.

STENOSIS OF THE DUODENUM: A STATISTICAL STUDY WITH THE REPORT OF A NEW CASE

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Congenital stenosis of the duodenum, which will be omitted from consideration in the present discussion, is properly classed among the rarer intestinal conditions. On the other hand, the acquired form occurs less infrequently than has been supposed by internists in the past, and it invariably develops secondarily upon morbid processes either in the duodenum or adjacent organs.

More or less extensive studies of the subject from various viewpoints have been made by Leichtenstern,[1] Perry and Shaw,[2] Wilms,[3] Boas,[4] Laffer[5] and others, but the clinical characteristics of duodenal stenosis have received less study than their importance warrants. A careful consideration of the subject has revealed a somewhat close and interesting relationship between this condition and such common causative affections, as duodenal ulcer and carcinoma, and disease of the head of the pancreas, as well as other adjacent structures.

But though numerous examples of stenosis of the duodenum will be presented hereafter, as the result of a statistical investigation, I venture to place the following new case on record, since it embraces certain details of interest and diagnostic value:

Mrs. S. B., aged fifty-six years, was admitted to the Medico-Chirurgical Hospital on January 5, 1912, complaining of pain in right hypochondrium

[1] V. Ziemssen's Handb. der spez. Path. u. Ther., 2 Aufl., Bd. vii, 2, 411.
[2] Guy's Hospital Reports, 1893, l, 171.
[3] Bruns' Beit. z. klin. Chir., Tubingen, 1897, xviii, 510.
[4] Diseases of the Intestines, 1901, 346.
[5] Ann. Surg., Philadelphia, 1908, xlvii, 1, 390 and 532.

and vomiting. Family history negative, excepting death of father from rheumatism. The patient had been in good health prior to four years ago, but since then has had several attacks of illness, which were diagnosticated acute gastritis. Habits were good, although she had used tea freely.

On December 21, 1911, following severe headache and a feeling of weakness, patient was seized with severe pain in right hypochondrium, which lasted about three minutes. This pain was not referred, but recurred three or four times daily, apparently without relation to the time of the ingestion of food, until date of admission to the hospital, and was somewhat relieved by vomiting. Following the first attack of pain, jaundice was noticed. After coming to the hospital, her condition showed marked improvement for a time; the attacks of pain and vomiting ceased, and the jaundice diminished considerably. There was some tenderness in the right hypochondrium and a small mass was palpable, which did not move with respiration. An *x*-ray examination did not reveal gallstones, but showed the pylorus to be in relation with the gall-bladder region, suggesting adhesions.

An examination of the urine revealed a trace of albumin, a small amount of bile, a trace of indican, and a few narrow hyaline casts. Cammidge reaction negative. A blood count on January 6, 1912, showed erythrocytes, 3,860,000; hemoglobin, 80 per cent.; and leukocytes, 11,600. Repeated examinations of the feces gave negative results.

On January 17, 1912, an examination of the gastric contents extracted one hour after a test breakfast gave the following result: Reaction, acid; total acidity, 60; free HCl, 0.1 per cent.; lactic acid, negative; pepsin, present; starch digestion, stage of erythrodextrin; occult blood, negative; bile, negative; mucus, a small amount.

Up to this time the patient's condition had been improving, but now vomiting recurred. There was no recurrence of the pain over the gall-bladder region, but the patient vomited frequently large quantities of bile-stained fluid. On January 23 there occurred a severe chill, and the pulse became more rapid and feeble. The temperature pursued a very irregular course, varying from a subnormal level to $101\frac{3}{5}$° F. An examination of the blood at this time showed a leukocytosis of 25,200; the differential leukocyte count resulted as follows: Polymorphonuclear cells, 81 per cent.; small lymphocytes, 7 per cent.; large lymphocytes, 11 per cent.; eosinophiles, 1 per cent.

On January 26, Dr. Ernest Laplace operated and found the duodenum markedly adherent to the under surface of the liver, and kinked at the site of adhesions. Situated between the duodenum and the liver was the much shrivelled gall-bladder. It was necessary to tear away liver tissue in breaking up the adhesions, leaving an excavation in the liver, considerable hemorrhage resulting. The gall-bladder could not be liberated from the duodenum, and owing to the patient's weakened condition, it was deemed

advisable to desist before the operation was completed. The patient died three days later, and necropsy was refused. The stenosis of the duodenum in this case was due partly to the constricting cicatrix of an old ulcer and partly to the kinking occasioned by the adhesions. Among other points of interest presented by this case are compression of the gall-bladder and common duct, apparently due to the adhesions, either old or recent, accompanied by jaundice, and indications of a secondary acute inflammatory process obviously occasioned by perforation of the duodenum at the site of an ulcer.

The further discussion of the subject of duodenal stenosis will be considered here in three aspects: (*a*) The incidence of the condition, including a collective investigation into the cases recorded in medical literature; (*b*) the etiologic and pathologic causes, and (*c*) the diagnosis.

(*a*) In 1898 Albu was able to collect only 43 cases from the literature, while Moynihan (1912) reports 56 cases from his own personal experience. I can report a totality of 262 collected cases. Albu's 43 cases, referred to above, were not added to those found in the literature in the present investigations, for the reason that this author's original paper could not be found. It should be stated, however, that 71 instances embraced in my statistics were recorded prior to the publication of Albu's article, and it is quite probable that these include many or all of his collection.

No cases of duodenal disease, which were found recorded in the literature, in which any doubt of actual stenosis existed, and of which there were many, are embraced in my series. In determining the existence of duodenal stenosis, I have been guided by either postmortem evidence or that revealed by operation, with a single exception, in which the notes left no room for doubt as to the diagnosis. The accompanying table (Table I), which is largely self-explanatory, sets forth the names of the reporters and the references, the pathologic causes, whether the latter are intra- or extraduodenal, and also whether benign or malignant. Again, the presence or absence of kinking is noted, and other points of unusual interest will be found in a separate column.

TABLE I.

Reporter.	Reference.	No. of cases.	Cause of stenosis.	Remarks.
A. de Haen	Rationes medendi, 1763, vi, 19	1	Compression by head of pancreas	Nature of pancreatic disease not mentioned.
Fullet	J. Univ. et Hebd. de med. et de Chir. Prat. Par., 1833, xiii, 33	1	Carcinoma of duodenum	Stomach enormously distended; perforation just below papilla.
Mondiere	Archives générales de Paris, 1836, 2, xii, 134	2	Carcinoma of pancreas	One case showed almost complete obstruction. Pancreas three times natural size in Case 2.
Holscher	Hannoversche Ann. f. d. gessamte Heilkunde 1840, Band v, 350	1	Carcinoma of head of pancreas	Complete for distance of three inches, not admitting goose quill.
Tanner	Prov. Med. Jour., 1842	1	Carcinoma of head of pancreas	Lumen size of goose quill.
Teisser	Jour. de Lyon, Nov. 11, 1847	1	Carcinoma of head of pancreas	Obstruction complete.
Chomel	Gaz. des Hôp., 1852, xxv, 37	1	Carcinoma of duodenum	Stenosis admitting little finger.
Arrachard	Gaz. des Hôp., 1860, 98	1	Carcinoma of duodenum	Stenosis almost complete.
Haley	Pacific Med. and Surg. Jour., San Francisco, 1873, 4, vii, 136	1	Carcinoma of duodenum	Stomach greatly distended; growth involving entire duodenum between pylorus and papilla.
Markoe	Tr. N. Y. Path. Soc., 1876, i, 265	1	Carcinoma of duodenum	Carcinoma six inches below pylorus, stercoraceous vomiting.
Reynolds	Tr. N. Y. Path. Soc., 1876, i, 266	1	Carcinoma of duodenum	Stomach dilated; vomited large quantities.
Descroizille	France Méd., 1876	1	Carcinoma of duodenum	Stenosis complete.
Salomon	Charite Annalen Jahrgang, 1877, iv, 144	1	Carcinoma of head of pancreas	Compressed ductus choledochus; extended into and caused ulceration of duodenum.
Dickinson	New York Med. Jour., 1879, xxx, 149	1	Carcinoma of duodenum	Extending from pylorus to jejunum and reducing duodenum to size of goose quill.
Rosenbach	Verhandlungen der Deut. Gesellsch. f. Chir., xi. Congress, 1882, 135	1	Gangrene of pancreas	Supra-papillary compression by peri-pancreatic abscess.
Cahn	Berl. klin. Woch., 1886, No. 22	1	Sarcoma of lymph glands	Enlargement of retro-peritoneal lymph glands compressing descending portion.
Gerhardi	Virchow's Archives, 1886, Band cvi, 303	1	Carcinoma of head of pancreas.	
Riegel	Zeitschr. f. klin. Med., 1886, xi, 187	1	Gallstone	Gallstone at mouth of common duct, permitting bilious reflux into stomach.
Hagenbuch	Deutsch. Zeitschr. f. Chir., 1887, Band xxvii, 1 u. 2, 110	1	Cyst of pancreas	
Hagenbuch	Deutsch. Zeitschr. f. Chir., 1887, Band xxvii, 1 u. 2, 110	1	Hematoma of pancreas	
Mason	Boston City Hospital Records, B. C. H. (unpublished), cclxiii, 26, cclv, 154	1	Carcinoma of duodenum	Opposite papilla; upper two inches duodenum dilated twice usual size.
Whittier	Boston Med. and Surg. Jour., 1889, cxxi, 377	2	Carcinoma of duodenum	In one case growth acted as valve, permitting regurgitation of intestinal contents.
Reiche	Jahrbuch d. Hamburger statskranken anstalten, 1890, ii, 180, Case I	1	Peritoneal adhesions	Infra-papillary, admitting little finger.
Reiche	Jahrbuch d. Hamburger staotskranken anstalten, 1890, ii, 180, Case II	1	Carcinoma of duodenum	Infra-papillary.
Hochhaus	Berl. klin. Woch., 1891, 17, 409, Case I	1	Pressure of gallstone	Stenosis just below pylorus; perforation of gall-bladder and pressure due to stone; stomach dilated.

TABLE I—(*Continued*).

Reporter.	Reference.	No. of cases.	Cause of stenosis.	Remarks.
Hochhaus	Berl. klin. Woch., 1891, 17, 409, Case III	1	Kinking due to adhesions	Partial stenosis of pylorus; another stenosis at lower end of duodenum; no tumor nor thickening of duodenum.
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	6	Duodenal ulcer	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	4	Carcinoma of duodenum	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	2	Peritoneal adhesions	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	5	Carcinoma of pancreas	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	1	Carcinoma of liver	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	4	Adhesions about gall-bladder	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	4	Morbid growths	At least two of these growths were of lymphatic origin.
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	1	Blood clot	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	1	Aneurysm	
Perry and Shaw	Guy's Hospital Reports, 1893, l, 171	1	Kinking	
Lange	Ann. Surg., Phila., 1893, 588	1	Duodenal ulcer	
Fenwick	Cancer and other tumors of Stomach, 1893, 291	2	Carcinoma of duodenum	
Herhold	Charite Ann., 1894, xix	1	Peritoneal adhesions	
Pye-Smith	Tr. of Path. Soc., London, 1894, xlv, 63	1	Carcinoma of duodenum	
Schule	Berl. klin. Woch., 1894, No. 45	1	Gallstone	
Pic	Rev. d. Méd., Paris, 1894, 1081; and 1895, 56. Obs., viii	1	Carcinoma of duodenum	"Growth" produced narrowing.
Mikulicz	Arch. f. klin. Chir., 1895, Band li	2	Obstruction by gallstones	Stones in diverticuli of cystic duct, which crossed and compressed duodenum.
Herz	Deutsch. med. Woch., 1896, No. 23, 362, Case I	1	Peritoneal band (tuberculous)	Stenosis complete; tuberculosis of peritoneum.
Herz	Deutsch. med. Woch., 1896, No. 23, 362, Case II	1	Cyst of head of pancreas	Infra-papillary stenosis; stomach not dilated; epigastric distention and pain, both relieved by vomiting of green material.
Herz	Deutsch. med. Woch., 1896, No. 24, 379, Case III	1	Gallstone	At first, symptoms of supra-papillary stenosis, later those of infra-papillary, supposedly due to change of position of stone.
Herz	Deutsch. med. Woch., 1896, No. 24, 379, Case IV	1	Carcinoma of duodenum	Infra-papillary stenosis; tumor small, constricting duodenum.
Wilms	Bruns' Beit. z. klin. Chir. Tubin, 1897, xviii, 510	1	Carcinoma of tail of pancreas	Caused infra-papillary stenosis.
Rewidzoff	Arch. f. Verdauungskr., Berl., 1898, iv, 369	1	Duodenal ulcer	
Wegele	Münch. med. Woch., 1898, No. 16	1	Obstruction by gallstones	
Aaron	Phila. Med. Jour., Feb. 4, 1899, 280	1	Carcinoma of duodenum	Supra-papillary, encircling duodenum.
Fenwick	Ulcer of Stomach and Duodenum, 1900, 45	2	Duodenal ulcer	
Siegel	Mitt. a. d. Grenz. d. med u. Chir., 1901, viii, 216	2	Carcinoma of pancreas	Infra-papillary.
Boas	Diseases of Intestines, 1901, 303	1	Carcinoma of duodenum	Supra-papillary.
Boas	Diseases of Intestines, 1901, 346	2	Impacted gallstones	Stones protruded from opening of common bile duct.

TABLE I—(*Continued*).

Remarks.	Reference.	No. of cases.	Cause of stenosis.	Remarks.
Boas	Diseases of Intestines, 1901, 350	2	Duodenal ulcer	Descending portion of duodenum; first portion much dilated.
Ochsner	Tr. Amer. Surg. Assoc., 1905, xxiii, 314	15	Sphincteric action of hypertrophied muscle	Infra-papillary; duodenum dilated; attributed to over-action of muscle, which normally retains chyme until mixed.
Delore	Lyon Méd., 1905, cv, 446	1	Duodenal ulcer	Gastric dilatation.
Eve	Brit. Med. Jour., Lond., 1905, ii, 117	1	Duodenal ulcer	Stricture admitting tip of index finger one and one-half inches below pylorus.
Davis	Tr. Chicago Path. Soc., 1905, vi, 345	1	Duodenal ulcer, probably tuberculous	Admitting tip of little finger; stomach dilated; tuberculosis of spleen and epididymis.
Mackenzie	Jour. Amer. Med. Assoc., Aug. 4, 1906, 341	6	Duodenal ulcer	Advocates plastic operation on duodenum in case of "hour-glass contraction."
Eckersdorff	Münch. med. Woch., Oct. 30, 1906	1	Duodenal ulcer	Near pylorus and mistaken clinically for pyloric stenosis.
Gray	Scot. Med. and Surg. Jour., 1907, xx, 35	1	Duodenal ulcer	Mentions stenosis as urgent indication for operation; stenosis may be marked; probe passed with difficulty.
Bernheim	Amer. Med., April, 1907, 234	1	Duodenal ulcer	No operation or autopsy.
Leo	Deutsche. med. Woch., 1907, xxxiii, 1279	1	Not determined	Located below papilla; regurgitation of bile and and pancreatic juice into dilated stomach.
Bidwell	The Hospital, Lond., 1907, xlii, 547	1	Duodenal ulcer	Dilatation of stomach.
Laffer	Ann. Surg., Phila., 1908, xlvii, I, 390 and 537	27	Compression by root of mesentery	Found in 120 autopsies of 217 cases of acute dilatation of stomach from literature.
Codman	Boston Med. and Surg. Jour., 1908, clviii	1	Compression by root of mesentery	Causing chronic dilatation of stomach
Deve and Beaurain	Méd. Mod., Paris, 1908, xix, 314	1	Compression by root of mesentery	
Mitchell	Tr. Roy. Ac. Med. of Ireland, 1908, xxvi, 76	1	Duodenal ulcer	Stomach dilated.
Berard	Lyon Méd., 1909, cxiii, 283	1	Duodenal ulcer	
Sourdel	Bull. et mém. de la Soc. de Anat. de Par., 1910, lxxxv, 230	1	Peritoneal adhesions	Compression by peritoneal adhesions and infected lymphatic glands.
Abadie	Arch. Provin. de Chir., 1910, xix, 287	1	Ovarian cyst	
Cumston	Internat. Clin., 1911, vol. i, 21st ser., 139	1	Adhesions	
Cheney	Amer. Jour. Med. Sci., Mar., 1911, 328	1	Duodenal ulcer	Frequent vomiting.
Johnson	Ann. Surg., 1911, ii, 197	1	Band of adhesions	Operated three months previously for jaundice; repeated attacks of pain, vomiting, and fever.
Burke	Surg., Gyn., and Obstet., October, 1911	1	Duodenal ulcer	Two marked constrictions due to multiple ulcers; and causing hour-glass duodenum.
Mayo, W. J.	Ann. Surg., 1911–12, 313, and personal communication	55	Duodenal ulcer	Occurred in 553 cases of duodenal ulcer.
Bassler and Grant	Amer. Jour. of Gastro-enterology, Phila., April, 1912, 15	1	Carcinoma of duodenum	Duodenum thickened and contracted throughout; pancreas enlarged, hard and nodular.
Moynihan	"Duodenal Ulcer," 1912	56	Duodenal ulcer	Found at operation on 287 cases of duodenal ulcer.
Anders	Amer. Jour. Med. Sci., September, 1912, 360.	1	Kinking	Kinking due to adhesions to liver, resulting from duodenal ulcer.

(*b*) The relative frequency with which stenosis of the duodenum is occasioned by one or other of the primary etiologic conditions is clearly indicated by the subjoined Table II, since it is believed that my figures furnish a trustworthy basis. It is worthy of note that by far the greater number—215 out of a total of 262 cases—are due to benign conditions, hence are in most cases, at least, amenable to timely surgical treatment. It is a matter of considerable interest that 185 or 70.88 per cent. of the cases were intra-duodenal in origin, and only 76 or 29.12 per cent. extra-duodenal. Cumston[1] found that compression outside the duodenum was by far the most frequent etiologic factor, but according to my own researches, this is true only after the exclusion of duodenal ulcer. Among the extra-duodenal conditions, which operated to produce stenosis were, diseases of the pancreas, compression by the root of the messentery, adhesions, morbid growths, kinking, gallstones, and of many others a single instance. The principal intraduodenal causes were ulcer of the duodenum, carcinoma of the duodenum, sphincteric action of the muscular layer and gallstones.

TABLE II.

Causes of stenosis.	Cases.	Percentage.
Ulcer of duodenum	140	53.44
Compression by root of mesentery	29	11.07
Carcinoma of duodenum	23	8.78
Carcinoma of pancreas	16	6.11
Sphincteric action of muscular layer of duodenum	15	5.73
Adhesions	12	4.58
Gallstones	9	3.44
Growths	4	1.53
Kinking	3	1.14
Cysts of pancreas	2	.76
Diseased head of pancreas (nature not mentioned)	1	.38
Hematoma of pancreas	1	.38
Gangrene of pancreas	1	.38
Ovarian cyst	1	.38
Carcinoma of liver	1	.38
Sarcoma of lymph gland	1	.38
Blood clot	1	.38
Aneurysm	1	.38
Not determined	1	.38
Total	262	

As stated above, gallstones may also operate by compressing the duodenum from without, *e. g.*, when they occupy a diverticulum in

[1] International Clinics, i, 21st series, 139.

the cystic duct. As a glance at Table I will show, stenosis due to kinking is rare, the numerical proportion being 3 to 262 cases. It is to be recollected, however, that in cases that come to necropsy without previous operation, kinking may not be recognizable, so that the condition may be more common than is indicated by these figures.

(*c*) In 1879 Leichtenstern[1] first called attention to certain symptoms, most of which are still recognized as being of major diagnostic importance in stenosis below the ampulla of Vater—namely, the absence of meteorism, the presence of biliary but never fecal vomiting, and early anuria.

The cases are, for convenience of clinical study, divisible into four groups:

1. Those due principally to kinking of the gut. The diagnosis of duodenal obstruction due to kinking is always difficult, and in most cases quite impossible. The condition may be attended with colicky pains in the epigastrium, which often recur regularly from three to five hours after meals. A duodenal kink is, as was true of my case, occasioned usually by adhesions, which have been produced by an ulcer and other lesions. If the kink be located above the ampulla of Vater, it excites symptoms practically identical with those of pyloric stenosis, with this difference, however, that the former develop acutely, as a rule.

On the other hand, when the topographic position of the kinking is below the ampulla of Vater, as was true of my case, a prominent feature is oft-repeated vomiting of biliary secretion. In respect of its clinical indications, the condition also bears a close resemblance to cholecystitis, and acute stenoses of the same portion of the organ of intra- or extra-duodenal origin, *e. g.*, compression by the root of the mesentery as the result of ptosis of the intestines.

In cases due to kinking, as in the case I herewith report, the vomiting may develop suddenly, be oft-repeated, causing shock, and lead to exhaustion of the system. This symptom is less menacing to life in the commoner types of stricture of organic origin, since these induce a more gradual narrowing of the duodenal lumen than

[1] Loc. cit.

kinking. The painful paroxysms referable to the right epigastric region are also both more severe and more frequent in acute stenosis than in more slowly developing types of the condition.

The points of difference here referred to (severer pains, more frequent vomiting, shock) may serve to separate the acute condition due to kinking and other causes, from the chronic varieties of stenosis at least. The early recognition of the nature and significance of the indications of acute obstruction developed upon certain chronic processes is, for the sake of timely operative intervention, of the utmost importance.

2. Suprapapillary duodenal stenosis. When due to the more slowly acting causes than kinking, stenosis above the ampulla of Vater cannot be separated from pyloric constriction, as a rule. In cases in which a contracting ulcer has been the cause of the stenosis, there is usually a clear history of pain from one to several hours after having taken food, and that the pain was relieved by vomiting, the latter symptom occurring one to two hours after the pain came on.

3. Stenosis at the ampulla of Vater. Cases in which the obstruction is situated opposite to Vater's ampulla can be accurately diagnosticated during life, as a rule, although their characteristic symptoms differ in certain particulars from those of either infra- or supra-papillary stenosis. Healed duodenal ulcers, when situated at the orifice of the common duct in the duodenum, may obstruct both the pancreatic and common bile ducts, producing chronic jaundice and progressive emaciation. As pointed out by M. Wilms,[1] obstruction to both the discharge of the pancreatic juice and bile into the duodenum will naturally cause acholic stools with consequent jaundice, and feces rich in fatty elements. The usual gastrointestinal symptoms dependent upon the absence of the biliary and pancreatic secretions likewise ensue. In these cases marked dilatation of the stomach and of the duodenum above the seat of the stenosis usually occurs.

Boas[2] reports two cases in which the diagnosis of high calculous obstruction of the duodenum was made and verified by operation.

[1] Loc. cit. [2] Ibid

In these instances of high incarceration of hepatic calculi in the common duct the stone partly compressed the duodenum and partly protruded into its lumen. Neither blood nor bile were found in the vomitus and the stomach was dilated. Jaundice was present, and the stools were acholic and contained enormous numbers of fatty acid crystals.

4. Stenosis below the ampulla of Vater. In the more usual chronic type of infra-papillary stenosis of the duodenum, besides pain and vomiting of much biliary matter, other characteristic features are present. For example, the stools may show an absence of the coloring matter of the bile, being clay-colored, and, as Boas has pointed out, may at times present a lime-like consistence. Constipation is marked. Jaundice may be in evidence, although the greater number of the cases recorded failed to show this symptom.

An analysis of the gastric contents by Boas, Riegel[1] and his pupil Honigmann,[2] and others, showed that free hydrochloric acid is usually absent in the infra-papillary variety, even in non-malignant stenosis; this is evidently ascribable to a free reflux of the alkaline intestinal juices from the duodenum to the stomach. In my case the percentage of free HCl present was about normal, but the gastric contents were not examined during the period of biliary vomiting. The absence of two symptoms should be noted here, namely, intestinal meteorism and fecal vomiting.

It may happen, however, as in the case recorded by Lemoine,[3] that duodenal stenosis is bound up with narrowing of the transverse colon, in which cases of fecal vomiting may be present. Dilatation of the stomach may occur, but is inconstant in infra-papillary stenosis. The epigastrium may be prominent, but the bowels are empty, as a rule. The epigastric distention subsides promptly, with relief from pain and oppression when present, after free emesis, but reappears in consequence of further regurgitation of bile and pancreatic secretion from the duodenum into the stomach. Herz[4]

[1] Zeitschr. f. klin. Med. 1886, xi, 187.
[2] Berliner klin. Wochenschr., 1887, No. 18.
[3] Bull. et Mém. de la Soc. Méd. des Hôp. de Paris, 1894, xi, 775.
[4] Deutsch. med. Woch., 1896, No. 23.

emphasizes a green color of the vomitus as having much diagnostic significance. This opinion was corroborated by the color appearance of the vomitus in my own case. Stenosis of the jejunum cannot be distinguished from infra-papillary duodenal stenosis. Finally, the latent character of certain cases of partial chronic stenosis of the duodenum must be recollected.

THE ABSORPTION OF FAT FROM THE BLOOD BY THE LIVER

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In a paper read before the Harvey Society of New York, three years ago, the view was advanced that fat circulating in the blood stream, unless it is removed and deposited unchanged in the connective tissues, is taken up by the liver and there prepared for use in other organs, desaturated and possibly built up into the complex phospholipines which are found in all the organs of the body.

This view was based to a large extent on indirect evidence, but in part also on the fact that if oils with a high iodine value, such as cod-liver oil, are given to animals, the fatty acids obtained by saponifying the fats of the liver have a much higher iodine value than is otherwise the case, and also than those obtained from other organs.

The attempt has been made to get further direct evidence for this view by the use of another oil with other properties. Cocoanut oil has a very low iodine value and yields on saponification fatty acids with a low mean molecular weight, 212, because it contains much of the glycerides of the acids of the acetic series with 10, 12, and 14 carbon atoms respectively. These acids distil much more readily with steam than the higher members of the series. The sample of this oil used in the experiments to be referred to yielded under the conditions adhered to throughout these experiments, 40 per cent. of its acids to a current of steam, the mean molecular weight of the acids that distilled over was 190, and they absorbed no iodine. In order to see how readily the presence of these acids in the liver of a cat could be detected, the livers of a number of normal cats were

heated with potash and alcohol, the fatty acids set free and distilled in a current of steam. The amount of acids obtained in the distillate was (1) 0.1 gm., (2) 0.108 gm., (3) 0.12 gm.; the amount of iodine absorbed by them was (1) 65.7 mg., (2) 62.3 mg., (3) 56.2 mg.; their mean molecular weight, 272. A cat's liver treated in the same way to which 1 gram of cocoanut oil was added gave 0.424 gm. of acid in the distillate, absorbing 49 mg. of iodine. If, as the results when no oil was added indicate, the liver alone would have given 0.1 gm., about 0.3 gm. of volatile acid was obtained from the 1 gm. of added oil, or about 80 per cent. of that which would have been obtained had this oil not been mixed with the liver. The iodine absorption points indeed to the yield having been higher than this. It was thus shown that there was a fair chance of detecting the presence of the acids of cocoanut oil if they were taken up by the liver.

The experiments consisted in the first instance of a series in which cats were fed on the oil for longer or shorter periods. In four cats it was found that the liver contained instead of only 1 dg. from 2 to 6 dg. of volatile acids, and that the molecular weight of these acids was low in proportion to their amount, 220, *e. g.*, when 6 dg. were found.

In a second series an emulsion of the oil in normal saline prepared by addition of lecithin or egg white was slowly run into the jugular vein. The coarser drops of the emulsion were stopped in the lungs, but without causing respiratory distress. The amount found in the lungs was deducted from the total amount introduced into the circulation, and the amount found in the liver, after deducting the amount that is normally to be obtained from it, formed a large proportion—30, 40, or 50 per cent. of the total introduced into the systemic circulation.

In a third series oil or the fatty acids obtained from it was introduced by a cannula into the small intestine, the lower end of which was divided and connected to a burette. Although in this way it is easy to demonstrate the absorption of considerable quantities of protein digestive products, it has proved difficult to observe the conditions that are necessary for the absorption of the fatty substances. Many different kinds of emulsions were tried, but the

only experiments in which clear evidence of absorption having taken place was obtained were two, in which the fatty acids were exactly neutralized with soda and the soap solution introduced; in these cases 3 and 3.6 dg. respectively were found in the liver, or 40 and 45 per cent. of the amount absorbed. But the soap solution caused damage to the mucous membrane. In a third experiment a small quantity of oil was absorbed when emulsified with bile salts and glycerin and secretin was given. In this case the increase in the volatile acids obtained from the liver corresponded to 50 per cent. of the oil absorbed.

Experiments done on dogs confirm those with cats so far as the infusion of oil emulsified by casein solution is concerned; of 6.7 gm. that reached the systemic circulation, 40 per cent. was found in the liver, as determined by the excess of volatile acids obtained from this liver over the amount obtained from normal dogs' livers. But in a number of feeding experiments in dogs, in which amounts varying from 3 to 20 gm. of the oil were taken up from the alimentary tract, the amount of volatile fatty acids found in the liver was small, corresponding to from 0.3 to 0.8 gm. only of the oil. The explanation of this result and its bearing on the interpretation of the results obtained by infusion is at present being investigated; the experiments with full data will be published elsewhere when they are completed. But the infusion experiments seem to confirm the inference drawn from experiments on the feeding of cod-liver oil, that fat that enters the general circulation is taken up by the liver in a way that points to this organ being specially concerned with the first stages in the metabolism of fats.

TERTIARY SYPHILIS OF THE LIVER

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There is a peculiar importance attached to the recognition of late syphilis in that diagnosis may mean and determine the issue between life and death. This is most strikingly shown in the tertiary lesions of the nervous system, but it also applies to syphilis of the liver. The symptoms caused by it are often serious and without diagnosis the issue may be fatal, whereas with its recognition and proper treatment we have in the majority of cases a demonstration of one of the most brilliant results of therapy. It is the recognition which is so important and therefore the clinical features are especially considered in this paper.

The study is based on 56 cases which were admitted to the medical service of the Johns Hopkins Hospital. The cases of early congenital syphilis are not included; they form a group well recognized and are not considered here. The cases regarded as late congenital syphilis are included.

The incidence of tertiary hepatic syphilis is difficult to state with any accuracy. These 56 cases occurred among 27,500 general medical cases, and it does not seem unlikely that an unknown number were overlooked. Among 3300 autopsies at the Johns Hopkins Hospital there were 46 of well-marked syphilis of the liver, but in many of these there were no clinical manifestations. Rolleston[1] quotes 64 cases among 11,629 autopsies at St. George's Hospital, London, and Flexner[2] 88 cases among 5088 autopsies at the Philadelphia

[1] Diseases of the Liver, 1905.

[2] New York Med. Jour., 1902, p. 10.

Hospital. It is probable that the condition is more common than is generally recognized.

Etiology. The essential etiological factor does not require discussion. The contributing factors were as follows.

Age. The distribution by decades was:

1 to 10	1
11 to 20	2
21 to 30	11
31 to 40	19
41 to 50	16
51 to 60	4
61 to 70	3

The three cases below the age of twenty years were regarded as instances of late congenital lues. The age of onset in these was three years, thirteen years, and sixteen years. The oldest patient in the series was aged seventy years.

Color. Of the series, 34 were white and 22 colored. This shows an unusually high percentage among the colored patients, the ratio being 1.8 to 1, whereas in the medical service of the hospital the figures are about 5 to 1.

Sex. This shows a preponderance of males, there being 41 males and 15 females. The number of colored females is striking, 10 out of the 15 females being colored. There were only 12 colored males. The explanation of the incidence in males may lie in the greater prevalence of syphilis, although this may not apply in the colored race, but it is of interest to inquire the effect of over-indulgence in alcohol.

Alcohol. The 3 patients below the age of twenty can be excluded. Of the cases in which there was a definite note as to alcohol, in only 4 was there no history of drinking. Of 37 with a definite history, in only 3 was the record of slight use; 19 described themselves as moderate users, and 14 had taken it to excess. This is rather striking and shows a very high percentage of moderate or heavy users of alcohol. It may be a factor in determining the occurrence of hepatic syphilis, not, however, meaning by this that syphilis is engrafted upon alcoholic cirrhosis.

History of Syphilis. In the 3 congenital cases there was a positive history of syphilis in the father of 1; in the other 2 the

history was very suggestive, as both mothers had had several miscarriages. In the adults there was a definite history of a primary infection in 26. In 9 others syphilis was suggested by a history of iritis, sore throat associated with eruption, miscarriages, etc. The time which had elapsed since the primary sore in the cases with a positive history varied from four to twenty-five years. There were 3 cases with an interval of four years and 3 with five years. With an interval of from six to ten years inclusive there were 7 cases, from eleven to fifteen years 8 cases, from sixteen to twenty years 3 cases, and from twenty-one to twenty-five years, 2 cases.

Morbid Anatomy. There were 46 cases among 3300 autopsies. The changes may be classified as cirrhosis, cicatrices, and gummata. Naturally there are various combinations of these. Of these 46 cases, in 23 there were changes described as cirrhotic; 19 showed cicatrices, and 21 gummata. In 8 cases there was a combination of gummata and cirrhosis, in 5 gummata and cicatrices, in 1 cicatrices and cirrhosis, and in 1 all three were present. In only four was amyloid change found. In 9 cases there were signs of syphilis found in other organs than the liver. In almost all the cases which came to autopsy the diagnosis was not made during life, the prominent features being due to disease elsewhere. In some a diagnosis was not possible, as there were no symptoms from and no signs of hepatic disease. Old scars in the liver cannot be recognized during life except in rare cases. The cause of death was very various: thus 14 died of cardiac and renal disease, 6 of pneumonia, 3 of acute peritonitis, 3 of tuberculosis, 2 of carcinoma, 2 of aneurysm, 2 of cerebral syphilis, and 1 each of gangrene, eclampsia, meningitis, accident, leukemia, etc.

Complaint. The study of the complaint made by the patient is of interest as showing the diversity of the symptoms for which relief was sought. Many of the patients had lesions other than in the liver. The most common was swelling of the abdomen, in 27 cases. Next in frequency was abdominal pain, usually referred to the upper abdomen, in 18 cases. Jaundice was the complaint in 7, shortness of breath in 5, loss of weight and strength in 3, vomiting in 2, fever in 2, and chills and fever in 3. In certain cases complaint was made of several of these conditions.

Previous History. The features which stand out prominently among the general symptoms are as follows: *Loss of weight* was the most frequent and had been more or less marked in 33 cases. The loss varied from fifteen to fifty pounds. Shortness of breath was marked in 10 cases and loss of strength in 9. Seven of the patients had suffered from fever, in 4 associated with chills. Two of the patients with chills and fever had been thought to have malarial fever and had taken large doses of quinine over long periods. In one case there had been chills and fever over a period of eighteen months. In several of the others a diagnosis of tuberculosis had been made, apparently based largely on the occurrence of fever without any obvious explaining cause. Three patients suffered from severe sweating not associated with chills or fever. Swelling of the legs was marked in 8, but in all was associated with ascites.

Features suggesting disturbance in the abdomen were common. Of these the most frequent was swelling, which occurred in 34 cases, and next abdominal pain in 28 cases. Indefinite gastric disturbance was a feature in 14 cases and vomiting in 14 cases; in 7 of these there had been hematemesis and in 2 melena. In several of the cases the hemorrhage from the stomach had been very severe. Diarrhea was marked in 3 cases. Jaundice occurred in 17 cases, in some being so intense that there was a greenish tint to the skin.

The duration of the symptoms when the patient came under observation varied from one month to eleven years. The duration was three months or less in 13 cases, three to six months in 11 cases, between six months and one year in 2, from one year to a year and a half in 14, about two years in 7, three years in 4 and eleven years in one. In the others the history was uncertain. In the longer periods the severity of the symptoms was not constant; there were times of improvement and remission.

Previous Ascites. This is of particular interest in regard to the general question of cirrhosis of the liver and its prognosis. Seven of the patients had previous attacks of ascites which had required tapping and after which there had been marked improvement so that they gave up treatment. In 3 patients, two of whom had been tapped four times, the intervening period was under a year. In 3

patients the interval had been about a year, the number of tappings being one, two, and seven. The remaining patient had been tapped eleven times eleven years before and 86½ liters of fluid removed, and sixteen times ten years before and 134 liters removed. In the intervals the condition had been fairly good. A striking feature in some of these cases was the good general condition despite ascites at intervals over a long period.

Pain. This was a marked feature in 34 cases. In 10 it was described as abdominal, in 12 referred to the epigastrium and in 7 to the upper right quadrant of the abdomen. In 2 it was described as in the right back; in 2 it was said to be in the liver itself, and in 1 referred to the region of the navel. Several of the patients complained of the pain being worse on lying down.

Bowels. No special features were shown. A few of the patients complained of diarrhea and a number described clay-colored stools.

Examination. The general findings are discussed first and then the special changes in the liver.

General Condition. A striking feature was *emaciation,* which was marked in 29 cases, and in some was extreme. A number of other patients had lost some weight but could not be described as emaciated. The appearance of many of the patients suggested severe illness. Jaundice was present in 23 cases. The degree varied from a slight to a marked jaundice, the color of three being greenish yellow. A striking feature was the rapidity of clearing of the jaundice under treatment.

Fever. There was some elevation of temperature in all but 7 cases of the series. This is a point of some importance in reference to diagnosis, as the persistence of fever had led to tuberculosis being suspected in some cases. The temperature in about two-thirds of the cases showed constant elevation. In the majority this was not very high, the record being 99° and 100° and 101° F. In some cases it was steadily between 100° and 102° F. In the other cases the temperature was not constantly elevated but rose each day. In the majority the highest point was not over 102° F., but in 3 cases it rose to 103° and 104° F. In some cases these elevations were accompanied by chills.

The influence of treatment on the fever was very marked in

almost all the cases in which fever was present. In one patient the temperature fell to normal in twenty-four hours and remained there, but the most common period required was forty-eight hours. This was observed in 11 cases. In 5 cases three days were required and in 5 other cases the temperature reached normal in 6 days or less. This result followed the administration of potassium iodide in the majority of cases; in some mercury was given also, but the most striking results were obtained with potassium iodide alone (Fig. 1).

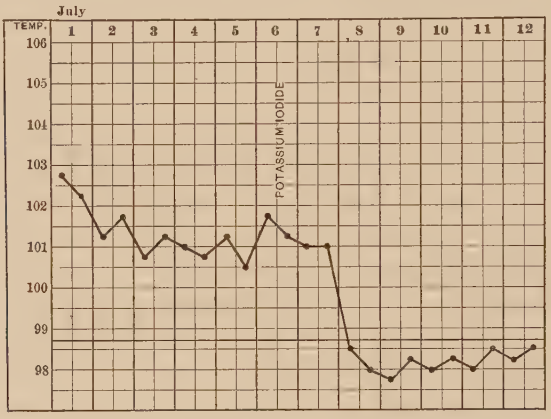

Fig. 1.—Showing the effect of potassium iodide on the fever.

Blood. The average count in 30 cases was hemoglobin, 71 per cent.; red cells, 4,380,000 per c.mm., and leukocytes, 8400 per c.mm. In 12 cases the leukocytes were over 10,000 per c.mm., the highest count being 13,000 per c.mm. In only 2 cases was the red count below 3,000,000, the lowest being 2,700,000 per c.mm. In 4 cases the count was between 3,000,000 and 4,000,000. The differential count showed some variation in certain cases, but there were no striking constant peculiarities.

Ascites. In 23 cases this was present and usually the fluid was large in amount. Tapping was done in 11 cases. This may seem a small proportion, but one of the striking features is the rapid disappearance of the ascitic fluid under proper treatment without tapping being required. Of the 11 patients one tapping was sufficient in four, four were tapped twice, one required to be tapped

three times and one was tapped thirteen times. The amount removed at one tapping varied from 2.5 to 22 liters. This last figure seems very large; the patient was admitted twice within six months and was tapped once on each admission, the amounts removed being 19 and 22 liters. She presented a remarkable appearance before each tapping and after it the improvement was striking. She was a colored woman who refused to remain in the hospital long enough to receive thorough treatment. The specific gravity of the ascitic fluid varied from 1008 to 1020 and the albumin content from 8 to 40 grams per liter. The predominant cells were small lymphocytes. In the only case in which the ascitic fluid was tested for the Wassermann reaction this was not given. Instances of a positive result have been reported.

Spleen. This was palpable in 24 cases, in the majority of which the enlargement was marked, in some the edge being several inches below the costal margin. In 8 other cases the area of dulness was increased. The spleen was always hard and firm; in no instance was any irregularity felt; in one case a splenic gumma was found at autopsy.

Liver. The changes in this organ are most important in the discussion of the subject. It is convenient to divide the cases into the congenital and acquired.

1. *Late Congenital Syphilis.* Of the late congenital cases there are three instances, which show considerable similarity in the findings. As Rolleston insists, we must be very careful not to mistake acquired cases for congenital ones. If acquired it must be at an early age and usually from accidental infection. In these three cases the age of onset of symptoms was two, twelve, and sixteen years. In the first case the mother had two miscarriages, but the child showed no sign of syphilis other than the hepatic condition. In the second there was chronic ear disease dating from the age of four and rhagades at the corners of the mouth. Three other children of the family died soon after birth. In the third case there was no other signs of syphilis, but the father had a syphilitic infection for which he had taken very little treatment.

In these cases the liver showed much the same condition. It was much enlarged generally, and showed remarkable large rounded

smooth swellings in the epigastrium which caused distinct prominences (Fig. 2). In one of the patients exploration was done and the mass was found to be a prominence on the surface of the liver which did not differ in appearance from the rest of the organ. It was distinctly softer than the liver tissue elsewhere, and there were many adhesions between it and the abdominal wall. A portion removed for examination showed some increase in connective tissue, but not much more. A positive Wassermann reaction was given by this patient and marked improvement for a time followed

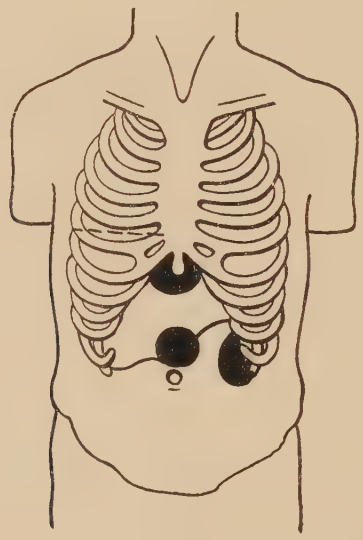

FIG. 2.—Large rounded prominences in late congenital syphilis. Enlargement of spleen.

the giving of mercury and potassium iodide. He died about four years later, and apparently from the resulting cirrhosis. In two of these patients there was in addition a small nodular mass felt on the right lobe. The spleen was much enlarged in two and the area of dulness increased in the other. All three patients had fever. Ascites was present in two of them.

2. *Acquired Cases.* In the study of the tumor one point is worthy of special emphasis, and that is the relatively marked involvement of the left lobe as compared with the right in many of the cases.

In 53 cases (three others being regarded as congenital) the liver was enlarged or showed a tumor mass in 49, and in 23 of these the involvement of the left lobe was strikingly marked in comparison with the right. This is an important point in diagnosis. In regard to the changes in the liver the cases may be divided into three groups.

(*a*) With general enlargement, but no marked gross irregularity of the surface (20 cases). In some cases the liver was slightly irregular.

(*b*) With definite nodules (20 cases).

(*c*) Showing a marked prominence which might be described as a boss sometimes associated with nodules elsewhere, but the large smooth enlargement being the striking feature (9 cases). In 3 cases regarded as late congenital this condition was present.

(1) *General Enlargement.* The extent of this varied from an edge which was two inches below the costal margin to cases in which the edge was below the navel (Fig. 3). The surface was smooth and the liver hard in the majority; in 2 cases the surface was slightly irregular. In 8 cases there was complaint of pain and tenderness on palpation. The spleen was enlarged in 12 cases and in 8 ascites was present. There was marked distention of the surface veins in 7 cases. Fever occurred in 14 cases. It is easy to see that ordinary cirrhosis would be suggested in the cases of this group. Actually, this mistake did not occur in the cases of this group. The incorrect diagnoses were: 1 was thought for a time to be hepatic abscess on account of fever, chills, and sweats, but the condition was recognized later; 2 had cerebral lues which dominated the picture; 2 had severe cardiac disease, to which the enlargement of the liver was ascribed.

(2) *Nodules.* In the majority these were particularly evident in the epigastrium or in the adjoining part of the right hypochondrium, 13 cases (Fig. 4). In 3 they were more or less general over the surface of the liver and in 3 there was a very large irregular nodular mass. Ascites was present in 10 cases. The spleen was enlarged in 14 cases. Prominence of the surface veins was marked in 8 cases. Fever occurred in 17 cases. The relatively marked involvement of the left lobe was marked in many of the cases of

this group. The error in diagnosis most to be expected would be neoplasm. This occurred in one case, exploration being done, which gave the diagnosis. In one case there was colloid carcinoma of the peritoneum; one was diagnosticated as hypertrophic cirrhosis until on a subsequent admission he returned with a tuberculous syphilide eruption; one had tuberculosis and the liver condition was regarded as amyloid (which was the case); and in one there was acute leukemia, the diagnosis of syphilis not being made until

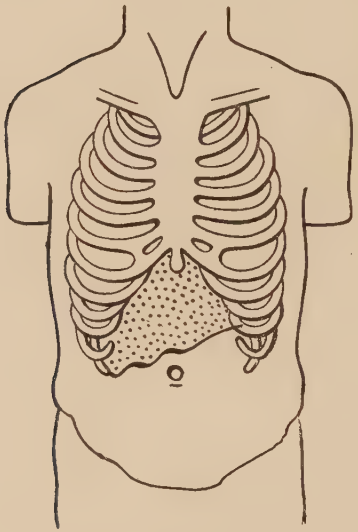

FIG. 3.—General enlargement of the liver, the surface having a slightly irregular character.

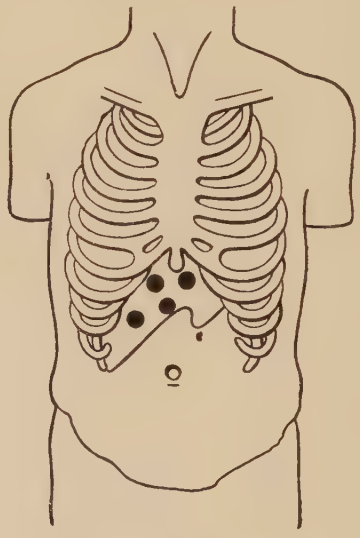

FIG. 4.—Nodules on the surface of the liver.

autopsy. Tuberculous peritonitis was the diagnosis in one case with ascites, the nodules in the epigastrium being regarded as a nodular thickened omentum.

(3) *Rounded Tumor.* The size was enormous in some cases, (Figs. 5 and 6), there being a large rounded projection which in some filled the whole upper abdomen. In several instances the enlargement of the spleen was remarkable; in 2 cases the organs practically touched and filled the whole of the upper abdomen. Ascites was present in 4 and the spleen was enlarged in 4 cases. In one a friction rub was heard over the mass. Fever was present in 7 cases. Only

one error in diagnosis was made, the enlargement being regarded as due to malignant disease. Survival for two years and the appearance of a luetic skin eruption (rupia) gave the correct diagnosis.

Diagnosis. This may give difficulty in three principal ways. In the first there is another condition, such as cardiac disease, which seems sufficient to account for the symptoms. This is especially likely to occur if the liver is not specially enlarged or if with enlargement the surface is smooth. In other cases ascites may prevent

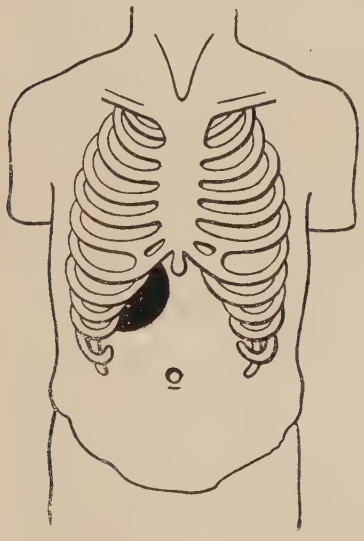

FIG. 5.—Large rounded mass projecting below the right costal margin.

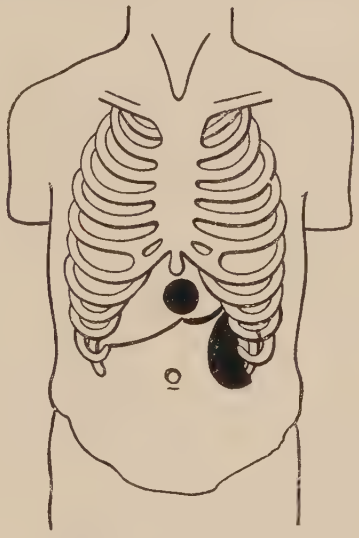

FIG. 6.—Large tumor with a rounded prominence. Marked enlargement of the spleen.

the recognition of hepatic enlargement. In the second group, disease of the liver is recognized, but its nature is not realized. In the third group some other abdominal condition, such as tuberculous peritonitis, is thought to be present.

1. In 8 cases some other condition was diagnosticated. In 3 cases there was cerebral syphilis, the symptoms of which were prominent. In 2 cases tuberculosis, and in the same number cardiac disease was present; in one acute leukemia. In all these the diagnosis was correct so far as it went. In one case the patient had tuberculosis, had been a heavy drinker, and alcoholic cirrhosis was suspected. In 2 cases there was advanced cardiac disease, and in the

remaining one leukemia was thought to be the cause of the hepatic enlargement.

2. There were 6 cases in this group. In 2 carcinoma and in 2 alcoholic cirrhosis were diagnosticated, and in one each, abscess and gallstones.

3. There were 4 cases, in 3 of which ascites was recognized, but its cause was not determined. In one carcinoma of the peritoneum and in one tuberculous peritonitis were suspected. One of the other cases was in some ways the most remarkable of the series. The patient was a colored man, aged forty-seven years, who complained of swelling of the abdomen and legs, which began one month before. There had been severe abdominal pain. There were ascites and edema of the legs, but the liver and spleen could not be felt. He died in three days after admission. At autopsy the liver was very irregular and showed a large mass of connective tissue which involved the hepatic vein and inferior vena cava. Many gummata were scattered through the liver.

It may be said that in several cases of 2 and 3 the correct diagnosis was made on subsequent examinations; in all of 3 it was made at autopsy.

General Symptoms. As is evident from the study of the symptoms there may be a marked change in the general condition. The patient may have lost weight and strength, be somewhat anemic, have had hematemesis and suffered from abdominal pain. Naturally the possibility of malignant disease comes particularly to mind. The occurrence of fever may suggest some infection. In the cases without any enlargement or evident change in the liver (only 4 in this series) only the knowledge of the possibility of syphilis of the liver, the search for proof of infection (especially the Wassermann test), and the results of specific treatment could give the diagnosis. In this connection the necessity of keeping syphilis in mind as the cause of more or less continued fever should be emphasized. It is very evident that with advanced cardiac or renal disease, tuberculosis, etc., in the absence of any special hepatic features the diagnosis is not likely to be made.

Recognition of the Liver Condition. Here there are several conditions which have to be considered, especially the diagnosis (*a*)

from ordinary hepatic cirrhosis, which is most likely to occur in the cases of uniform enlargement, (*b*) from newgrowth, either of the liver, or in some cases, in which there is a single nodule, from newgrowth of the stomach. This is most likely in cases with marked nodular changes in the liver. (*c*) In the cases with the large smooth dome-like tumor, abscess or cyst may be considered. (*d*) Ascites may give difficulty, and it is very important to palpate the abdomen immediately after tapping. It may only be possible then to feel an enlarged liver or a small nodule. Of less importance are (*e*) amyloid disease, (*f*) cholelithiasis, (*g*) splenic anemia, and (*h*) Hodgkin's disease.

There are some points which deserve emphasis in this connection. One is a history of previous tapping followed by improvement for a time. There were 7 such cases in this series. Another is the finding of relatively marked involvement of the left lobe as compared with the right. This, with any striking irregularity in the organ, should always suggest the possibility of syphilis. The features of the tumor are especially discussed.

(*a*) *Group with General Enlargement.* This is difficult to distinguish from ordinary cirrhosis, especially as many of the patients give an alcoholic history. Careful examination should be made for any nodular enlargement and this is particularly important immediately after tapping if there is ascites. In several cases a small nodular mass was felt coming from below the costal margin on deep inspiration, sometimes high up in the costal angle. The liver itself often feels very hard and the surface may be uneven and somewhat rough. Tenderness is sometimes quite marked. It is evident that the distinction from an ordinary cirrhosis is not easy. The knowledge of the possibility of syphilis is perhaps the greatest aid, as it suggests the Wassermann reaction and the therapeutic test. The value of this last is great and of course there need never be any hesitation in doing it, as no harm will result if the condition is not syphilitic. The following is an example of this group:

The patient was a woman, aged thirty-five years, who complained of fever. She had had pelvic infection with a double salpingitis for which both tubes had been removed sometime before. She gave a history of one

miscarriage. There had been fever for some months which varied from 99° to 101° F. She had lost considerable weight and at one time the diagnosis of tuberculosis had been made and then again of pelvic infection. At one time on account of the fever it had been thought that she might have typhoid fever and the Widal reaction had been done on two occasions, both negative. On examination the patient was emaciated and looked badly. There was no jaundice. The liver was found to be distinctly enlarged and the edge could be felt two inches below the costal margin in the right nipple line. Dulness above in the right nipple line began at the fourth rib. The liver was tender; no nodules were felt. The spleen was markedly enlarged; the edge was felt below the costal margin and was quite hard. There was no rash or evidence of any bone lesions. Diagnoses of typhoid fever, malarial fever, tuberculosis, and septic infection had all been considered. In view of the continued fever and enlargement of the liver it seemed important to consider syphilis. The Wassermann reaction was found to be positive. The patient was put on inunctions and given potassium iodide and on the third day the temperature dropped to normal and remained there. Within two weeks she had gained 8 pounds and the liver was definitely smaller in size and the edge could just be felt below the costal margin on deep inspiration. The spleen was reduced in size and the edge could just be felt on full inspiration. The patient was seen nine months later; she had gained 25 pounds in weight and looked the picture of health. Neither the liver nor the spleen could be felt.

(*b*) *The Group with Nodular Masses.* The diagnosis here may be very difficult and a nodule in the liver, particularly in the left lobe, may suggest malignant disease in the stomach or bowel or in the liver itself. As an example of the former the following is quoted:

The patient was a white male, aged thirty-one years. He came complaining of digestive trouble. He had a primary lesion eight years before but had taken very thorough treatment for five years. His present illness dated back one year. He began to feel badly, complained of pain in the epigastrium and a certain amount of nausea, but no vomiting. He had not been jaundiced. He had lost 25 pounds in weight and on examination was emaciated. There was slight fulness in the left epigastrium, and on palpation a small nodular mass could be felt which was quite tender. The edge of the liver was just felt in the right nipple line, but could not be positively felt in the median line. The spleen was not felt. After inflation of the stomach the nodule was more easily felt, but its situation was not changed. The note over it was tympanitic. Test meals showed a low total acidity with a mere trace of free hydrochloric acid. The blood count showed a secondary anemia.

The diagnosis was between newgrowth of the stomach and syphilitic nodule of the liver. It was very difficult to tell whether the mass was in the stomach or liver. It was decided to watch the effect of specific treatment and the patient was given inunctions of mercurial ointment and potassium iodide by mouth. The improvement was very striking; the nodule rapidly disappeared in size and could not be felt within a month. The patient gained weight rapidly and was soon in perfect health.

The masses on the liver may be regarded as evidence of malignant disease, a mistake which it is easy to make if the general features are marked. The following is such a case:

The patient was a white male, aged fifty-four years, who complained of swelling in the abdomen. His present illness had lasted for about a year and began with nausea and discomfort after eating. Jaundice appeared a few months later. He had lost a great deal of weight and there had been marked abdominal swelling. The patient was emaciated and anemic. The abdomen was much distended with a distinct prominence in the upper part on the surface on which irregularities could be seen. On palpation a hard irregular nodular mass was felt, with the lower edge considerably below the navel. A little to the left of the navel a definite notch was felt. The diagnosis of carcinoma was made. The patient did not live in Baltimore, and after discharge he was lost sight of for two years, when it was learned from his physician that the patient was still living and had a well-marked skin eruption, regarded as syphilitic.

In one case of this kind an exploration was done to determine the cause of abdominal symptoms, the patient having severe pain. Two gummata were found in the liver.

(*c*) A variety of other diagnoses may be made. Abscess of the liver may be suspected, particularly in the cases with chills, sweats, and irregular fever. Such a case is the following:

The patient was a white male, aged thirty-eight years, who came with a history of abdominal pain, great weakness, loss of 20 pounds in weight, and fever with sweating for the last six weeks. He had had a good deal of diarrhea. The patient looked very badly, was anemic and very sallow. He had several attacks of severe pain in the region of the liver, which was somewhat enlarged and quite tender. There was marked tenderness in the seventh interspace, a little outside the right nipple line. The temperature was very irregular, varying from 98° to 102.5° F., and the patient had a number of profuse sweats. Liver abscess was suspected and a number of

exploratory punctures were made over the right lobe of the liver, but nothing but blood was obtained. After this the patient was put on potassium iodide with which the improvement was rapid, the pain disappeared and he gained weight and was discharged well.

The *mistakes* in diagnosis which were actually made as regards the tumor are of interest. In other cases, as when cerebral syphilis was present, the diagnosis was correct, but the liver condition was not regarded as important or there was no enlargement of the liver. In 10 cases a wrong diagnosis of the liver enlargement was made. In 2 of these this was carcinoma; in one the diagnosis was corrected by the duration, the appearance of a specific skin eruption and the result of treatment; in the other case the patient had both carcinoma of the peritoneum and syphilis of the liver, as was found at autopsy. In two cases a diagnosis of hypertrophic cirrhosis was made; in one the patient returned a year and a half later with a tuberculous syphilide, following which the result of treatment was marked. In the second case syphilis of the liver was suspected, but excluded, as the Wassermann reaction was negative. Some months later, however, the Wassermann reaction was positive and the diagnosis was also supported by the result of treatment. One case was diagnosticated as cholelithiasis and the proper diagnosis reached through the result of treatment over a year later. In one case operation was done to determine the cause of persistent pain and enlargement in the upper abdomen, no positive diagnosis having been made. In one case abscess of the liver was suspected until the trial of specific treatment, which gave the correct diagnosis. Tuberculous peritonitis was the diagnosis in one, the nodules in the left lobe being regarded as the thickened omentum. Enlargement of the liver from cardiac disease was regarded as the cause in one case; this was present and hepatic syphilis as well. In the last of this group practically every possible diagnosis was made by different men. This was regarded as an instance of late congenital involvement and in many particulars was like a remarkable case reported by Cheney.[1] Hanot's cirrhosis, angioma, adenoma, Hodgkin's disease, and cyst were all considered in addition to cirrhosis. Even

[1] Jour. Amer. Med. Assoc., March 26, 1910, liv, 1053 to 1056.

after the abdomen was opened it was not possible to be sure of the diagnosis. A positive Wassermann reaction and the response to specific treatment gave the correct diagnosis.

Therapeutic Test. There must always be some risk of error in trusting to the result of therapy to make a diagnosis, but in this condition the results are so striking that it has to be included as a method of diagnosis. We have both the general effect, shown particularly on the fever, and the local changes in the liver. As already noted, the effect on the fever is usually very striking, in many cases the temperature falling to normal within forty-eight hours. The influence on the liver itself is almost equally marked; two or three weeks may show a marked decrease in the size of the liver as a whole or of prominences on its surface. In some cases the spleen also showed a remarkably rapid decrease in size. While sometimes the enlarged liver in cirrhosis may show a rapid decrease in size, yet this is not likely to cause confusion.

A knowledge of the condition must be regarded as the most important aid to diagnosis. Other signs of syphilis may suggest the diagnosis. The presence of unexplained fever with hepatic symptoms should suggest syphilis and doing the Wassermann reaction. If in doubt the therapeutic test should always be tried.

Course. Judging from autopsy experience, recovery must be comparatively common. So far as we can decide the hepatic functions are completely restored, as in many patients dying of other diseases and having extensive changes in the liver from syphilis there is no evidence of any disturbance. It is just as certain that a certain number die of the disease and the majority unrecognized. In cases with extensive cirrhotic changes the outlook is practically the same as in ordinary cirrhosis. In such cases we must not expect to do much by treatment.

There were fourteen deaths among this series of 56 cases. Of these in only one could death be attributed directly to hepatic syphilis. In this case the process caused obliteration of the hepatic veins and inferior vena cava with resulting thrombosis. In 5 cases death resulted indirectly, in 4 from the resulting cirrhosis, and in one from amyloid disease. Some of the patients with cirrhosis had received active treatment, with resulting temporary improve-

ment. In one case death resulted from carcinoma of the peritoneum, in 3 from chronic nephritis and uremia, in one from pulmonary tuberculosis, in 2 from cerebral syphilis, and in one from acute leukemia. In the other cases improvement was the rule as regards the liver condition. Several of these had other serious diseases, such as renal, cardiac, or pulmonary, which affected the general health.

Treatment. This is the usual therapy for syphilis, with special emphasis placed on the administration of iodide of potassium. In many of the cases this alone was given with a perfect result. No difference could be observed when mercury was added, but it seems wise to give both drugs. Dramatic results, such as almost immediate disappearance of the fever, reduction in the size of the liver nodules, and rapid gain in the general state and weight were seen when iodide alone was given. One patient gained 25 pounds in a month. Salvarsan was given to three patients in doses of 0.5 or 0.6 gram, and in two of these mercury and iodide were not given in order that the effect could be watched. Improvement followed in both cases, but not as rapidly as was the case with iodide alone or mercury and iodide. In the third case all three were given.

We must recognize that in some cases while we can influence the syphilitic process in the liver we cannot prevent or materially affect the resulting cirrhosis unless the cases are seen early and recognized.

Conclusions. 1. Syphilis of the liver presents a very varied clinical picture with prominent general symptoms in many cases, of which loss in weight is marked. The duration of the symptoms may be prolonged and there may be periods of improvement. Fever is a common occurrence.

2. There are features suggestive of hepatic disease in the majority of the cases. Enlargement or tumor is the most common. This may suggest other conditions, especially malignant disease. General enlargement and the occurrence of nodules or large rounded masses are the most common. A striking feature is the relatively marked enlargement of the left lobe as compared with the right.

3. The diagnosis may be obscured by other diseased conditions, or the liver condition may be interpreted wrongly. Ascites is

sometimes a difficulty. Knowledge of the features of hepatic syphilis and the therapeutic test are important aids.

4. Treatment can influence the syphilitic process, but not its results (cirrhosis, amyloid).

DISCUSSION

Dr. George Dock: I think this is a very important subject, as Dr. McCrae has said, and I would like to pass around these *x*-ray prints to illustrate one side of it. Some years ago (1907), in discussing continued fever of obscure origin in this Association, I reported a case of syphilis of the liver which had been operated for gallstones. I recently saw another case in which I was able to help the patient by remembering my former experience. I have here the *x*-ray. This patient was a young man who had syphilis four years ago, had been thoroughly treated by a good man, and had several negative Wassermann reactions last year. He then developed liver pain and finally the diagnosis of gallstones was made and preparations for operation were about completed when the surgeon asked to have me come in to see the patient. I saw the patient, with a slight jaundice, but an enormous liver reaching from the fourth rib to the navel. At least one and one-half inches outside of the usual site of gall-bladder tumors was a large hard mass, not very painful, though the patient had nocturnal pain so severely that he had to have morphine for it. There was a very beautiful *x*-ray available, taken very much better than the photographs show. There was a very brilliant shadow, if you will pardon the expression, over the position of this tumor. A shadow that was so intense and showed so much density that I said I did not think it could possibly be gallstones because I had never seen a gallstone skiagraph that showed so distinctly. The *x*-ray operator afterward told me he thought the great density of the mass indicated gumma rather than gallstones. The result of the discussion was that the operation was postponed. The *x*-ray as well as physical examination showed a relatively large amount of swelling in the left lobe. The patient was immediately put on large doses of iodide, the nocturnal pains stopped almost at once, the liver went down, but the tumor remained as a stony hard mass in the same region, showing about the same resistance to *x*-rays. I regretted very much that I had to urge against operation. I would have given a great deal to see the patient's liver and to feel it better than I could through the abdominal wall, but I thought it was better to try the therapeutic test first. I think you will all agree that in these cases the therapeutic test is advisable.

Dr. M. Howard Fussell: Dr. Osler called attention to the facts regarding syphilis of the liver that Dr. McCrae alluded to, the great importance of keeping this condition in mind when we are dealing with enlarged liver. I am reminded of a case in the clinic of the University of Pennsylvania where a man came with a huge mass apparently in the left lobe of the liver, quite as large as an infant's head. Everybody thought it was certainly carcinoma. Upon administration of inunctions the shrinking of the tumor was almost miraculous. Before five weeks it had disappeared.

Dr. J. M. Anders: It has been well said that it is difficult at all times to recognize syphilis of the liver. Cases of syphiloma on the surface of the organ are, according to certain writers, rare. This does not accord with my personal experience, and I was not surprised to hear that Dr. McCrae met with an equal number as compared with the two other leading clinical varieties. With one or two exceptions the tumor has been attached to the left lobe of the liver in my cases. In a discussion of the subject of the diagnosis of hepatic syphilis it seems to me that mention might have been made of the importance of a clear history of primary infection and lesions elsewhere in the body. In addition to this I should like to point out that well-defined indentations along the edge of the organ are diagnostically important and have helped me in a number of instances. Again, the painless character of these tumor masses when due to syphilis and the fact that they do not change from week to week or from month to month even. With reference to late hereditary syphilis of the liver I have become convinced that the most reliable means we have of recognizing this form is the Wassermann test.

Dr. Theodore C. Janeway: This Association knows the interest my father always had in this question of tertiary syphilis, and there was one point in diagnosis he laid stress on, namely, the peritoneal friction due to the perihepatitis over the gummatous nodule which will usually be found if searched for. As to the ready response of liver syphilis to treatment, while this is the rule, I have seen one striking exception. This was in a woman, and the diagnosis lay between gumma and abscess. We were forced to give morphine on account of the very great pain and tenderness. She failed entirely to yield to the administration of iodide and mercury by mouth, and yet the liver swelling went down rapidly with intramuscular injections of mercury. That is the only case I remember which has contradicted Dr. McCrae's findings.

Dr. McCrae: We obtained a definite history of primary infection in 35 out of 56 cases. The interval varied from four to twenty-five years.

In reference to the severity of the pain, this was a prominent symptom in 28 out of 56 cases, and in many was so severe that gallstones and abscess had been suspected. Definite peritoneal friction rub was noted in only one case. It was probably not looked for in all cases. In regard to the question of therapy, in a case of syphilis of the liver in which the ordinary administration of mercury was not efficient it would be well to give it by intramuscular injection. There was no such case in this series.

DEFECTIVE DEVELOPMENT FROM ARTHRITIS IN EARLY LIFE

By GEORGE DOCK, M.D.
ST. LOUIS, MISSOURI

Chronic arthritis is rare in children, and this partly explains why many details are not as thoroughly known as is desirable. So, very few writers even mention the arrested development that might be expected from non-use or other causes in such cases. Osler quotes Still, who, in the first edition of Allbutt's System, vol. iii, page 104, in describing the disease sometimes called after him, says: "In cases beginning before the second dentition there is often a marked arrest of bodily development; a child twelve and a half years of age, in whom the disease began at four years of age still had the appearance of a child of six or seven."

Ollier first demonstrated that injury to epiphyseal cartilages causes retardation of long growth. Bidders and Vogt saw shortening after partial destruction of epiphyseal cartilages. J. Wolff showed that loss of growth in bones might occur far from seats of disease, *i. e.*, in the feet in coxitis. In contrast with these changes that seem not expected, Diamantberger and others have noted an enlargement of the great toes, which indicates a nutritional change of a less simple character.

I recently had a case under observation in which a youth of twenty-four, with a history of arthritis without heart lesion from the age of eleven, had slight general retardation as shown by puerile figure and expression with defective development of the long bones and relative or absolute shortening of the bones of the extremities. I anticipated an opportunity of thorough Röntgenologic and other

study of the bones and joints, but a terminal nephritis hastened the fatal end and an autopsy could not be obtained. It seems to me, however, that a report of the case may serve to direct attention to more thorough examinations in other cases, and that ultimately the processes involved may be explained:

Abstract of History

C. C., single, aged twenty-four years, white, newsman, admitted December 13, 1911, to Medical Clinic of Washington University Hospital; died January 7, 1912. No autopsy.

Abstract from St. Louis Children's Hospital records: First admission, September 22, 1900. "Two years ago patient had grip which resulted in rheumatism." Physical examination shows greatly enlarged and painful joints, especially the small joints. Diagnosis: Arthritis deformans, chronic. Second admission, October 1, 1901. Age, thirteen years. Diagnosis: Arthritis deformans. April 20, 1902, discharged; improved.

Present complaint, "rheumatism."

Family History. Mother is living and well; aged forty years. Father died of rheumatism at thirty-one. Had three brothers and one sister, all in good health. One brother had an attack of rheumatism six years ago, but recovered completely.

Personal History. Never was sick until he was eleven years old. "Rheumatism in ankles from wet feet and exposure" was first trouble. Had diphtheria, measles, and scarlet fever at Children's Hospital when about fourteen years old. Had mumps and whooping cough at about the same time. Had measles last and seemed to be in much better health afterward than he had been before. "Rheumatism" has been constant, but was less severe after measles. Was out of Children's Hospital for a year and a half, then went to St. Luke's Hospital; was there nine months and was much improved. Could get along very well with a cane when he left. Was not troubled much about walking for one year, then ankle was sprained and use of crutches begun. Has not been able to discard them since. Had gonorrhea four years ago; recovered in six weeks. Joints not affected at that time. He had occasional headache; nose has been partially obstructed since childhood. No pneumonia or bronchitis; no dyspnea; no pains in chest. No precordial pains or palpitation. Heart has never been said to be affected. Has had "indigestion" since two months ago. Patient thinks trouble is due to bad teeth; is sure it did not come from food. If too much liquid is taken vomiting occurs immediately after eating. Sometimes vomiting does not occur for an hour, and sometimes in the morning previous supper is vomited. Vomitus always consists only of food taken

at previous meal; often is bile-stained, but never has been stained with blood. If vomiting occurs several hours after eating the vomitus is scanty. A severe headache is always associated with vomiting. Headache stops in an hour after vomiting. Has no pain in stomach. Passes urine four to six times each night and once or twice during the day. No pain on urination. Large amount of urine of high color voided at night, but no great amount at one time. Urination is urgent and involuntary if closet is not reached at once. Muscles are very weak. Mental and nervous condition fairly good.

FIG. 1.—Photograph of patient showing his youthful appearance, the atrophy of the extremities and the extent of the arthritis.

Uses small amount of coffee and tea, also small amount of beer and

whisky, two or three drinks each week. Sleeps well; eats well. Has worked as newsboy and man on the street for several years.

Present disease, patient says, began in ankles after exposure and wet feet about thirteen years ago, at the age of eleven years. Ankles were swollen and stiff for a week or two, then swelling moved up the muscles of both legs to the knees, which became swollen, hot, and red. Swelling spread upward until shoulders and arms were involved. Nearly all of the joints are

FIG. 2.—Röntgenograph showing the changes in the bones and joints.

stiff and the muscles are very small and weak. There is no continuous pain, but pains shoot from one joint to another. No pain in muscles. Throat and neck swollen for about two months. Never has been painful.

Present condition. December 13, 1911. Patient is a sparely nourished young adult. Gums and mucous membranes pale. Pupils equal; react to light and accommodation. Ears and nose free of discharge. Marked swelling of tissue about neck and side of jaws, the normal lines being partially

obliterated. No tenderness, nor can any glandular structures be palpated. No fluctuation.

Tongue coated, breath foul. Teeth in poor condition—pyorrhea alveolaris; no general glandular enlargement; nasal obstruction.

Thorax long, costal angle narrow, expansion slight; better over right front. Percussion note clear in front and in axillæ, auscultation negative. Heart: maximum impulse in fourth interspace, just inside the nipple line, 7.5 cm. from midsternal line. Heart action regular; sounds clear all over; slight accentuation of second pulmonic. Radial pulse regular, 84 to minute.

Abdomen natural looking; moves well; no masses or tenderness. Liver dulness begins above at bottom of the fifth rib and ends one finger breadth below costal margin. Edge just palpable. Genitalia normal. Spleen not palpable.

Extremities. Marked atrophy in upper and lower extremities. There is fixation of right elbow and right wrist; marked thickening of middle phalangeal joints of both hands. On left there is good motion in left elbow-joint. There is ankylosis of both hip-joints and partial ankylosis of both knee- and ankle-joints.

Blood, December 14, 1911: red corpuscles, 5,200,000; leukocytes, 11,000; hemoglobin, 70; color index, 0.7.

Urine examination, December 13, 1911. Specific gravity, 1009; acid; cloudy; albumin, large amount; 1 per cent. by Esbach: sediment contains many hyaline, waxy, and cellular casts.

Note by Dr. Dock, December 15, 1911. Patient has an unusually youthful appearance; the arms and legs are poorly developed, the arms are very short (see measurements). The frame is juvenile but the body hair and external genitals are well developed.

The appearance of the patient is best appreciated from the photograph, but a few of the measurements are given (*A*), with the measurements of a normal individual of about the same height (*B*), and those from another case (*C*) of chronic arthritis, beginning at nine years of age with more marked fixation than the patient but without special developmental defect:

	A Cm.	B Cm.	C Cm.
Vertex to perineum	84.00	98	75.0
Vertex to navel	64.00	..	58.0
Clavicles	12.00	..	12.5
Shoulder to elbow	27.00	31	30.0
Elbow to wrist	18.00	25	18.0
Wrist to end of middle finger	16.25	18	18.0
Crest of ilium to trochanter	15.00	15	13.0
Trochanter to knee	36.5	40	35.0
Knee to external malleolus	35.5	41	34.0
External malleolus to sole	6.5	7	4.0
Length of foot	19.00	27	21.6

The excretion of urine became smaller, the stomach became so intolerant of food that enemata were used, and they, too, soon became impossible to retain. Later the patient became comatose, and died next day, January 6, 1912.

The changes in the bones and joints can be realized fairly well from one of the many Röntgenographs made by my colleague, Dr. R. D. Carman. The bones show rarefaction as is common in cases of chronic arthritis. Besides the erosion, cupping, and exostoses of the articulating ends, there is the not uncommon change in the shape of the heads of the bones, so that the heads of the humerus and femur and the condyles of the femur and head of the tibia seem elongated. The shafts of the long bones are unusually thin and slender and the metacarpal bones and phalanges have cupping and broadening of the articular surfaces and narrowing of the shafts, somewhat suggestive of achondroplasia. It seems to me impossible to exclude the latter process, but I present the case without further comment.

DISCUSSION

Dr. James B. Herrick: Dr. Dock's case calls to mind a case of mine of quite a different character, and yet perhaps somewhat related, which I saw before the days of *x*-rays. A woman had both elbows ankylosed, which ankylosis she said dated from an attack of smallpox in childhood. During that illness both elbows had been inflamed, and since then the forearms had grown but little. They were very short. I take it there was not only an arthritis but an epiphysitis occurring during the course of smallpox.

Dr. B. Sachs: I should like to call attention to the fact that the cessation of growth in the long bone occurs in conditions in which the joints are fixed, to be sure, but not from an arthritis, and that the general arrest of development of the extremity is very apt to occur. Take the cases of infantile hemiplegia which come on very early in life. It is a common experience in these cases to see a shortening not only of the long bones of the upper extremity of the two slides. Personally, I have had the idea that the mere disuse of the part seems to have some effect upon the continuance of normal growth of that part, and the question comes up in cases like Dr. Dock's arthritis, if simple disuse for many years has not had some similar effect.

ANTITYPHOID INOCULATION: THREE YEARS' EXPERIENCE WITH ITS USE IN TRAINING SCHOOLS FOR NURSES IN MASSACHUSETTS

By LESLEY H. SPOONER, M.D.
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Pfeiffer's experiment which led Wright to introduce antityphoid inoculation into the British Army was more far reaching than one could have imagined at that time. All are familiar with the extensive work which has been accomplished on these lines in the English, German, and United States Armies.

Inoculation material has been most varied. Heat-killed vaccines have been the most popular and in fact the only preparations used to any considerable extent in man. But animal experiments and a few human inoculations have been attempted with other material. Vincent[1] recommends macerated organisms sterilized by ether. Müller[2] has treated cultures with lecithin and extracted the product with chloroform. Rusznyák[3] has used the typhoid immune serum, while Besredka[4] and Bessau[5] have employed mixtures of the serum and dead organisms. Chemical agents, such as silver salts, glycerin, sodium carbonate, formalin, and carbolic acid, have been widely used to sterilize cultures. Macfadyen[6] has employed frozen, powdered, and filtered organisms. But the most extreme method is that of Castellani,[7] who employs on his third and fourth injection living organisms which have been attenuated by an exposure to 50° C. The advantages and disadvantages of these methods, although worthy of prolonged discussion, cannot be considered at the present moment.

All practical work has been accomplished in artificial typhoid immunity by means of heat-killed vaccines. Pfeiffer and Kolle[8] and Wright[9] recommend heating to 60° C., but Leishman[10] and Russell[11] advise only 53° C. In my work I was guided by the

careful researches of Major Leishman and others of the British Commission,[10 12 13] whose work alone at that time seemed complete.

It is well recognized that the typhoid bacillus is the greatest foe to the soldier in the field. During the last century nearly all the armies of the civilized world have been devastated by this infection, but the dangers of typhoid communication were not fully realized until the discovery of the specific organism by Eberth in 1880, and its demonstration in the various excreta of the body which followed very shortly.

It was shown by Joslin and Overlander[14] that the nurses of Massachusetts were eight times more liable to typhoid infection than others less intimately associated with the sick. For the ten years ending 1908 two to four nurses contracted typhoid fever each year in the Massachusetts General Hospital alone. According to my statistics[15] there was a morbidity of 1.4 per cent. among the nurses, as compared with Joslin's of 1.41 per cent. among the nurses of most of the large hospitals of Massachusetts. This unnecessary prevalence of typhoid fever in the best regulated of our hospitals caused Dr. Mark W. Richardson, Secretary of the State Board of Health, who had long been interested in the disease and its prevention, to bring the matter before the Governing Boards of the Massachusetts General Hospital. Their response was prompt and decisive, so that inoculation was started there at once and has been continued regularly to the present time.

In order to produce immunity in such a class of individuals it was necessary to demonstrate the safety of the process and the relative ease with which it could be accomplished. To bring about this result I proposed the use of small doses, frequently repeated, of a low virulence vaccine. My vaccine material was and still is essentially the same as that used by Leishman and Russell.

Technique. In my work the technique is briefly as follows. The stock culture was isolated from the spleen of a case of typhoid fever in 1902, so that its attenuation has been considerable. Its killing power with animals is four times less than that of a similar culture only one year old. The organisms, grown on agar slants for twenty-four hours, are killed by an exposure to 53° C. in the water bath for an hour. Standardization is made with the Zeiss

blood platelet counter. Injections are four in number, and are given at five day intervals. The doses, which vary somewhat with the size of the individual, are 100,000,000, 200,000,000, 400,000,000 to 600,000,000. For small women and children the amount of the vaccine is proportional to the body weight.

The site of injection is preferably in the left interscapular region, but many inoculations have been performed at the insertion of the left deltoid. The latter seems less convenient because of the considerable muscular activity in the neighborhood of the swelling which occurs in almost all instances. Alcohol is used as a local antiseptic. When large numbers are to be inoculated at one time several syringes are used which are boiled between injections, care being taken to cool the syringe before vaccine material is introduced.

Reaction. It is a well-recognized fact that debilitated people present the most profound reactions, and I have observed that latent and chronic disease of a non-typhoidal character may be made active by an inoculation. I have avoided vaccination in such individuals, especially tuberculous patients, but I have suffered a few accidents through improper histories. In this way a temporary, but not serious, acute exacerbation has taken place in three chronic arthritides, a chronic cholecystitis, a subacute urethritis, and quiescent cases of furunculosis and acne. The duration of these untoward effects was very short, however.

The safety of my work necessarily calls forth a discussion of the "negative phase" so strongly supported by Wright, Morgenroth, and Vincent. Since many of the nurses are exposed to the disease during inoculation, a period of diminished resistance would be of great danger. Pfeiffer, Leishman, and Russell have shown that the period following injection is one of increased resistance, however. This is in perfect accord with the small morbidity of typhoid among these nurses and 80 others who were most intimately exposed to the disease before and during inoculation. In this light it is an interesting and important fact to note that those few who were inoculated during the incubation period presented a milder form of the disease than those from whom the infection arose.

The reactions have been reasonably slight. Locally the site of inoculation presents a tender, painful wheal. When a vein is accidentally punctured a more severe local reaction results, the

swelling and ecchymosis persisting several days. The neighboring lymphatic glands may become enlarged and tender. The duration of the latter symptom is very short, however, and the local soreness rarely lasts more than twenty-four to thirty-six hours. The constitution reaction in my latest personal cases, some four hundred in number, is as follows:

	Per cent.
Absent or slight	86
Moderate, *i. e.*, malaise, headache, and fever not exceeding 100.5°	10
Severe, *i. e.*, vomiting, diarrhea, chills and fever reaching 102° to 103°	4

These symptoms last from twelve to twenty-four hours, rarely forty-eight hours. Furthermore, in only five instances has a moderate or severe reaction been produced in any individual by more than one of the four inoculations. Fifty per cent. of the moderate reactions followed the second injection, the first and third dividing the remainder nearly equally. Among the severe reactions, 50 per cent. were produced by the third, the first and second dividing the remainder. Only very rarely does the fourth inoculation produce any discomfort. I have observed that when inoculation is started on the eve of catamenia or during the early days of flow, that constitutional reactions are apt to be more severe. As a result, I plan so far as possible not to have the first two injections fall within those days.

Hospital Inoculation. During the first year my work was limited to the Massachusetts General Hospital, but since that time inoculations have been performed by me or under my supervision among the nurses and others intimately exposed to the disease in twenty-three hospitals in Massachusetts, through the efforts of Dr. Richardson. In all 1585 individuals have received this treatment. The result of hospital inoculations is told in a word by the following table:

Individuals inoculated in hospitals	1361
Individuals uninoculated (but exposed) in same hospitals	674
Cases of typhoid among the inoculated, excluding 3 who were inoculated during the incubation period	3
(1 of these was a paratyphoid infection)	
Cases of true typhoid among inoculated	2
Cases among the uninoculated	17
(9 of these were paratyphoid cases)	
Cases of true typhoid among uninoculated	8
Morbidity among inoculated	0.15 per cent.
Morbidity among uninoculated	1.19 per cent.

The last figure is somewhat lower than those of Joslin and the writer quoted above. But it shows what may be expected among such large numbers of nurses unprotected by inoculation. The marked reduction among the inoculated needs no further comment. The two cases contracted among the inoculated occurred in the following manner. One, a year following inoculation, had cared for two fatal cases of typhoid without her hospital. Her disease was severe, but was followed by recovery. The other, two years after inoculation, while caring for several cases, received in the mouth some typhoid material. Although the mouth was washed with antiseptics a mild infection followed.

In the Massachusetts General Hospital, where inoculation has been in progress for three years, and where over 80 per cent. of the nurses and others exposed to typhoid have been protected, no cases of typhoid fever have been contracted. The following table illustrates exposure in the medical wards during the typhoid season of 90 nurses who have completed their course and 92 who are still in training.

	Average months of typhoid duty.	Average months of typhoid night duty.	Percentage of nurses serving night duty during typhoid season. Per cent.
Pupils	2.42	0.54	42
Graduates	2.88	0.64	47
Total	2.64	0.59	44

The high percentage of inoculated nurses serving night duty during the typhoid season is most suggestive, since that class furnishes most of the cases of the contracted disease. In all fairness it must be stated, however, that rather fewer cases of the disease have been treated in the hospital during this three-year period. But this reduction is in no way proportional to the decrease of the incidence above noted.

Blood Changes. Agglutination reactions have been performed by the microscopic method because of its ease, accuracy, and its moderate value. The first hundred cases showed positive reactions in the following dilutions two weeks following inoculation:

	Per cent.
1 to 50 or greater	80.6
1 to 25 or greater	94.2

Macroscopic agglutination reactions at an equal interval show positive results varying between 1 to 1000 and 1 to 10,000. This quality of the blood persists to a considerable degree for two years, but is still evident after two and one-half years (Fig. 1).

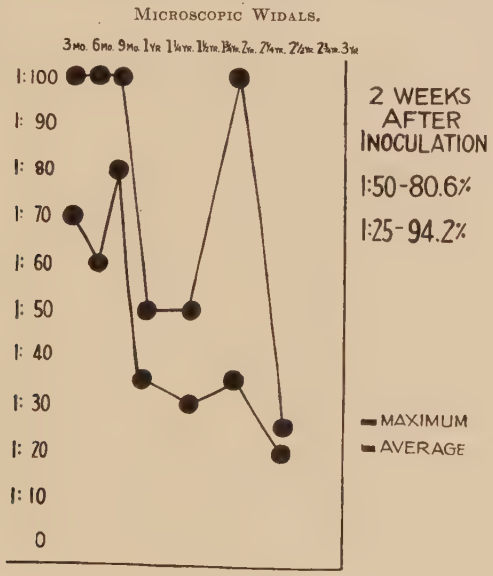

FIG. 1

That an immunity exists in the presence of a positive agglutination reaction of even mild degree is most reasonable. But the converse is not true, since all are familiar with the usual transient character of the antitropic substances of the blood following an attack of the disease itself. Further investigations of blood changes, *i. e.*, bacteriolysins, opsonins, etc., have not been carried out, since those points are now well established.

EPIDEMICS. The employment of this treatment in epidemics has been very meagre. This has been due no doubt to the fear of the so-called "negative phase." It has been attempted twice by me. In one instance the infection proved to be paratyphoid; and the results, though interesting, are of no great value. They are as follows:

	Per cent.
Morbidity among inoculated	6.6
Morbidity among uninoculated	12.0

These figures are somewhat striking, since each class embraces an equal number of individuals. Over 80 per cent. were inoculated during the incubation period, a fact which detracts considerably from the value of the statistics. But in spite of this there is a considerable reduction of morbidity and only two cases appeared after inoculation was completed. Inoculation during this epidemic was of very doubtful value.

Greensboro Epidemic.

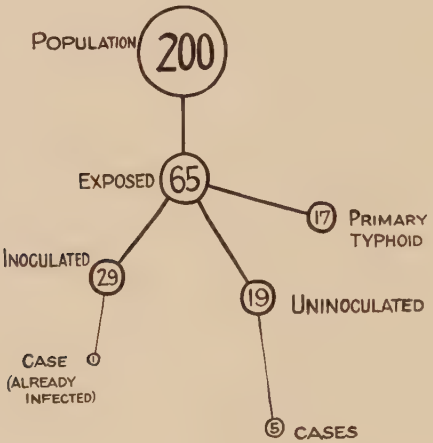

Fig. 2

The second epidemic was of greater interest and the results proved more satisfactory. The water supply of a limited number of people in a little Vermont village became contaminated with the typhoid organism from the excreta of an isolated individual who had died from the disease six months prior to the epidemic. The original primary cases, 17 in number, appeared simultaneously. Within a week 29 of the remaining 48 who had been exposed to the disease through the water supply had been inoculated; 19 remained uninoculated. Among the latter 5 cases developed; among the former 1. The latter presented his first symptoms immediately following his first inoculation. His disease was of a very mild variety (Fig. 2).

The small size of this epidemic forbids drawing too broad

conclusions, but it seems rational to advise the employment of this treatment, since no harm appears to result when the vaccine is given in a judicious manner. Furthermore, the absence of cases contracted among the inoculated in this epidemic and in several isolated cases of immediate exposure seems to be far from a coincidence. Inoculation in the time of epidemics must be performed with care, since it is nevitable that many must be inoculated during the incubation period. The result of this accident is not serious, however. My experience would indicate that the onset of symptoms was hastened by this step, but that the infection was shorter and of a less severe character, possibly because of the destruction of organisms before they had multiplied to a sufficient extent to produce a natural reaction from the unassisted body.

Including this epidemic and other personal cases the final statistics are as follows:

Inoculated individuals	1585
Uninoculated individuals	700
Cases among inoculated (excepting those mentioned)	2
Cases among uninoculated (with similar exceptions)	13
Morbidity among inoculated	0.12 per cent.
Morbidity among uninoculated	1.86 per cent.

Conclusions. Frequent injections of small amounts of a low virulence vaccine cause slight inconvenience.

They seem to produce a protection among nurses, who are eight times more liable to the disease than the average individual.

Their morbidity, under ordinary conditions, is 1.4 per cent. or 19 cases among 1361.

Only two cases developed under these conditions.

Case morbidity among the uninoculated is nearly nine times greater than among the inoculated, subjected to similar conditions.

No permanent untoward effects have arisen from over 5000 injections.

The blood picture indicates a certain protection lasting at least two and one-half years.

The use of this means of protection has been shown to be safe in two epidemics and very efficient in at least one of them.

NOTE.—I am deeply indebted for their careful work in completing subsequent inoculations and for excellent records to Dr. E. M. Crane, of Hardwick, Vermont, and to those physicians in charge of the Hospitals in which inoculation has been introduced.

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DISCUSSION

DR. WILLIAM H. PARK: We had a very interesting case in our laboratory along the line of the case Dr. Spooner reported. A girl swallowed by mistake a few cubic centimeters of a bouillon culture of typhoid bacilli. She was one of the laboratory workers. I immediately immunized her, but she came down at the usual time and was a case of moderate severity. One other point; by accident three persons got 4,000,000 bacilli for their first immunizing dose; one had no appreciable reaction, the second had a slight reaction, and the last had a very severe reaction, the symptoms lasting for five days.

MAJOR FREDERICK F. RUSSELL: I have had a case like Dr. Park's; the man pipetted a living culture into his mouth; he was given a mouth wash of liq. cresolis comp. and vaccinated, and did not become infected. I have been especially interested in the statement of Dr. Spooner as to his use of antityphoid vaccine during an epidemic in Vermont, and at the Massachusetts General Hospital where typhoid is present at all times of the year. To establish the fact that we can immunize safely in the presence of an epidemic is very important. The belief in a negative phase which carries with it increased susceptibility to infection has been the

greatest objection to this form of prophylactic immunization. Wright believed in it and preached it widely, and it has done more than anything else to hold the movement back. Last year in Torrington, Connecticut, there was a typhoid epidemic due to a contaminated water supply. One of our Corps happened to be there, and induced his friends to use vaccination immediately. Many persons were vaccinated, including 45 of the 80 nurses. Not one of the vaccinated persons developed the disease, while 3 of the 35 unvaccinated nurses contracted it during the next two months. Thus we have another instance showing that it is perfectly safe to vaccinate in the presence of an epidemic. We know pretty well now from experience that vaccinating against typhoid does not carry with it any danger. We have vaccinated to date about 150,000, and the only accident has been one case of temporary musculospiral neuritis. We know that this vaccination does protect. Our experience on the Mexican border last year proved this definitely. We know that the immunity does not begin to fall off until between two and three years, and in that way it compares favorably with the immunity conferred by vaccinia. We do not yet know its duration. The question of its use in certain classes of people is of some interest. I have been immunizing a good many children and young people, school children, and people who were going from a healthy city to the country. We all know that the liability to infection in the large cities of the North is very slight, yet we send children to the country and go ourselves to regions where the typhoid rate is many times higher than at home. Children and young people rarely have unpleasant reactions, and they can easily be protected by immunization against a real danger.

Dr. M. H. Fussell: During the last winter the supply pipe which ran to the Twenty-first and Twenty-second Wards of Philadelphia broke. They immediately pumped raw Schuylkill water into the main, which spread quite an extensive epidemic of typhoid fever in these two wards. It so happens that I was in St. Timothy's Hospital where we received 35. I immediately vaccinated all my nurses, which happened to be eighteen; none of the nurses developed typhoid and none of them a very severe reaction.

Dr. Mark W. Richardson: This work of Dr. Spooner's is especially interesting to me because it represents a continuance of investigations which I made for a number of years at the Massachusetts General Hospital. The fact that nurses acquired typhoid fever from time to time had been well known for a number of years, but the exact incidence was unknown until, at my suggestion, Dr. Spooner looked up the figures for the ten years previous to 1910 and found that during each year of that period anywhere from two to six nurses came down with typhoid fever.

The situation seemed so serious that at my suggestion the nurses were

called together and the question of specific inoculation was put before them. An unexpectedly large number volunteered for inoculation. Then, as secretary of the State Board of Health, I sent a circular letter to all training schools for nurses in Massachusetts, with the results which you have heard from Dr. Spooner. I have used these vaccines in the treatment of typhoid fever in perhaps 40 or 50 cases, but I have not been able to convince myself certainly as to the efficacy of this treatment. I believe, however, that these vaccines, if intelligently used, will prevent a large per cent. of relapses. Furthermore, certain observers have thought that vaccines would eliminate the typhoid carriers. This has not been proved, however. Incidentally, I may remark that the Massachusetts Legislature has recently given power to the State Board of Health to manufacture specific material for typhoid inoculation for the use of the physicians of the Commonwealth, and it is probable that this material will become available within the next few months.

Dr. Spooner: The reaction from excessive doses is not always proportional to the amount of vaccine material employed. The smaller doses, however, are justified on the one hand by a universally less severe reaction, and on the other by the distinct protection afforded. Major Russell has spoken of the increased likelihood of typhoid among travellers. This is becoming recognized widely by those contemplating European trips. But, unfortunately, the practice of this means of prevention is far less common among travellers in this country than the fact justify. A lamentable fact in connection with hospital inoculation in Massachusetts is the tendency to neglect this treatment until cases of the disease have already arisen among the hospital personnel. The folly of this short-sighted policy is obvious.

A RESEARCH ON THE EXPERIMENTAL TYPHOID-CARRIER STATE IN THE RABBIT

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Blachstein, in 1891,[1] showed by his experiments that the gall-bladder in rabbits inoculated intravenously with typhoid bacilli might afford a harbor for the typhoid organisms for a prolonged period. He also showed that the infection in the rabbit soon passed into the chronic stage, as evidenced by the great loss of weight and strength. At that time nothing was known of the so-called "typhoid carrier." It occurred to the writer that a condition allied to the typhoid carrier state in man might be induced in the rabbit, and remedied by means of vaccine treatment.

Since 1891 numerous experimenters, Forster and Kayser,[2] Doerr,[3] J. Koch,[4] Chiarolanza,[5] and Morgan,[6] among others, have worked along these lines, but from their researches very little knowledge of the chronic condition of infection as found in the rabbit has been added to that learned from Blachstein's original work.

Some investigators, notably Conradi,[7] Hailer and Rimpau,[8] have succeeded in freeing inoculated rabbits from typhoid bacilli by the intrarectal injection of chloroform; but I believe the use of a typhoid vaccine has not previously been advocated, except by Stone,[9] who reports two human carriers treated by injection of a typhoid vaccine, with success in one instance.

Since November, 1911, the writer has experimented with 28 rabbits, inoculating them all with the same amount of inoculum, viz., 0.5 c.c. of a suspension of a twenty-four-hour agar culture of

Bacillus typhosus in sterile normal salt solution (0.85 per cent.) injected intravenously. The blood and feces were examined from day to day after the first week following inoculation. Prior to plating on Endo medium (Kendall and Day modification),[10] the blood and feces were incubated for twenty-four hours in sterile beef bile. Suspicious colonies on the plates were then fished at the end of eighteen to twenty-four hours and tubes of Russell's[11] double sugar medium inoculated for confirmation. In case of doubt the Hiss serum water media were used and the agglutination reaction tested. The animals were divided into four series. The detailed results follow.

FIRST SERIES

All the animals were inoculated December 5, 1911, with 0.5 c.c. of the suspension above mentioned.

No. 1. Weight, 1940 grams. Vaccinated. Blood and feces were examined December 11, 14, January 2, 5, 11, 15, 17, 19, 24, 27, 29, 31, February 12, 20, March 5, 16. Vaccinated January 11, and 16, 1912 with 20,000,000 dead organisms at each injection. The blood contained Bacillus typhosus until January 17, the feces until January 24; thirty-six and forty-three days respectively. Agglutinins, December 19, 1 to 200; January 17, 1 to 600, March 5, 1 to 100. Killed March 20, weight, 1550 grams; loss, 390 grams. The gall-bladder contained 0.5 c.c. of thin straw-colored fluid, the walls were slightly thickened. No eroded areas. Cultures of blood, spleen, gall-bladder wall, bile, feces, intestinal wall and urine were all negative for Bacillus typhosus.

No. 2. Weight, 1635 grams. Unvaccinated. Blood and feces were examined December 11, 14, January 2, 5, 11, 15, 17, 19, 24, 27, 29, February 12, 20, March 5, 16, 24. The blood contained Bacillus typhosus until January 16, the feces until March 24; thirty-five and one hundred and three days respectively. Agglutinins, December 19, 1 to 200; March 5, 1 to 200. Killed April 6, weight, 1270 grams; loss, 365 grams. Liver was large, pale in color, and on section showed signs of fatty change. Gall-bladder was small, and contained 0.4 c.c. of thick, curdy, yellowish-green fluid.

The wall was thickened and in places necrotic. The blood, spleen, gall-bladder wall, bile, feces and intestinal wall were cultured and Bacillus typhosus recovered from the gall-bladder wall solely. Microscopic examination of sections of the gall-bladder wall did not reveal the typhoid bacilli, but many inflammatory areas were found in the papillæ.

No. 3. Weight, 1465 grams. Vaccinated. Slight diarrhea December 7 and 8. Blood and feces were examined December 7, 8, 9, 10, 11, 14, 20, 27, January 2, 5, 11, 15, 19, 24, 27, 29, 31. Vaccinated with 15,000,000 dead organisms January 11 and 16. Blood contained Bacillus typhosus until January 19 and negative from then on except January 27, when typhoid bacilli were recovered. The feces contained Bacillus typhosus until January 27; forty-three and fifty-one days respectively. Agglutinins, December 19, 1 to 400; January 17, 1 to 800. Died February 1, weight, 900 grams; loss, 565 grams. No hyperemia of the intestinal mucosa or lymphatic enlargement was noted. Liver pale in color and showed marked coccidiosis. Gall-bladder contained 1 c.c. of thin, pale yellow bile in which were numerous flocculi. Gall-bladder wall was thickened and eroded in places. The blood, spleen, gall-bladder wall, bile, feces, intestinal wall and the flocculi were cultured and gave negative results for the Bacillus typhosus.

No. 4. Weight, 1295 grams. Unvaccinated. Blood and feces were examined December 12, 13, 15, 17, 20, 21, 30, January 5, 11, 16, 22, 24, 28, February 12, 20, March 5, 16, 25, April 10. No typhoid organisms were recovered from the blood until December 15; from then until January 21 it continued to be positive. The stools were positive from December 12 until February 22; from this time on no typhoid bacilli could be discovered in the feces; Bacillus typhosus was found in the blood and feces for thirty-eight and seventy-two days respectively. Agglutinins December 19, 1 to 200; March 5, 1 to 100. With a view to establishing a catarrhal condition in the gall-bladder and so causing a return of the organisms to the feces and possibly to the blood stream from their hiding place in the gall-bladder, repeated doses of eserine, gr. $\frac{1}{100}$, and pilocarpin, gr. $\frac{1}{8}$, were given but without effect. Finally on April 10, 15 c.c. of sterile beef bile were introduced into the stomach

through a catheter. Diarrhea ensued and the animal died in about six hours with marked toxic symptoms. Examination of the feces revealed the presence of the typhoid bacillus. Died April 10, weight 1520 grams, a gain of 225 grams. The gall-bladder was contracted, wall hyperemic, and contained 0.4 c.c. of a dark brownish-red, curdy fluid. The mucosa was injected, the gall-bladder wall was necrotic. There was marked injection of the bloodvessels of the intestinal mucosa throughout. The intestine contained liquid feces. Bacillus typhosus was obtained in pure culture from the gall-bladder wall and from the feces. Cultures from the blood, spleen, bile, intestinal wall and the urine were all negative.

No. 5. Weight, 1370 grams. Unvaccinated. Blood and feces were examined December 11, 14, January 2, 5, 11, 15, 17, 19, 24, 27, 29, 31, February 12, 20, March 5, 16. Blood and feces were both positive for Bacillus typhosus on December 11. Typhoid bacilli were recovered from the blood until January 14, and from the feces until March 24; thirty-three and one hundred and three days respectively. Agglutinins, December 19, 1 to 200; January 5, 1 to 200; March 5, 1 to 80. April 11 was given 1 c.c. of beef bile and received this dose daily until diarrhea was established on April 17. Feces were positive for Bacillus typhosus on this date, on April 18 and 20; negative on April 21 and 22. Killed on April 22, weight, 1300 grams; loss, 70 grams. Liver was pale in color. Gall-bladder was small and contracted, containing 0.5 c.c. of a dark, reddish-brown fluid. Gall-bladder wall was thickened; bloodvessels injected. Intestines contained liquid feces. Bacillus typhosus was recovered from the gall-bladder wall and feces.

No. 6. Weight, 1270 grams. Unvaccinated. Slight diarrhea December 7; feces examined culturally gave positive result for Bacillus typhosus. Blood and feces were examined December 11, 14, January 2, 5, 8, 11, 15, 23, 27, 28, February 12, 22, 27, 28, 29, March 5, 16, 25, April 10. Blood contained Bacillus typhosus until January 23, the feces until March 25; forty-seven and one hundred and nine days respectively. Agglutinins, December 19, 1 to 200; March 5, 1 to 100. Weight, May 4, 1150 grams; loss, 120 grams.

No. 7. Weight, 1280 grams. Vaccinated. Blood and feces examined December 11, 14, January 2, 5, 8, 11, 15, 17, 19, 22, 27, 28, 29, 30, 31. Blood was positive until January 11 and feces until January 28; thirty and forty-seven days respectively. Vaccinated January 11 with 15,000,000 organisms. Agglutinins, December 19, 1 to 200; January 17, 1 to 600. Died February 10, weight, 950 grams; loss, 330 grams. Liver was pale in color, showed fatty change and marked coccidiosis. Gall-bladder contained 0.5 c.c. of thin straw-colored fluid in which were numerous flocculi. Urinary bladder was distended. The blood, spleen, gall-bladder wall, bile, urine, feces, intestinal wall and liver were cultured and proved negative.

No. 8. Weight, 1540 grams. Vaccinated. Blood and feces were examined December 11, 14, January 2, 5, 7, 11, 15, 17, 19, 22, 24, 27, 28, 29, 30, 31, February 12, 20, March 5, 16, 25, April 10. Blood was positive until January 15, feces until January 24; thirty-four and forty-three days respectively. Vaccinated with 15,000,000 organisms January 11. Agglutinins, December 19, 1 to 200; January 17, 1 to 400; March 5, 1 to 200; April 15, 1 to 100. Weight, May 4, 1240 grams; loss, 300 grams.

SECOND SERIES

All the animals received the same inoculation as above mentioned, on December 27, 1911.

No. 1. Weight, 1472 grams. Vaccinated. Blood and feces were examined December 30, January 1, 8, 10, 14, 22, 31, February 7, 14, 16, 19, March 7, 16, 25, April 10, 27, May 4. Blood contained Bacillus typhosus from January 1 to February 11; feces, from January 1 to February 23; forty-two and fifty-four days respectively. Vaccinated February 8 with 20,000,000 organisms. Agglutinins, January 8, 1 to 200; February 8, 1 to 200; February 14, 1 to 500; March 20, 1 to 400; May 2, 1 to 100. Weight, May 4, 1680 grams; gain, 208 grams.

No. 2. Weight, 1360 grams. Unvaccinated. Blood and feces examined December 30, January 1, 8, 10, 14, 22, 31, February 1, 2. Blood contained Bacillus typhosus from January 1 to February 2 as did the feces; thirty-three days for each. Agglutinins,

January 8, 1 to 300. Died February 3, weight, 850 grams; loss, 510 grams. A slight hyperemia of the intestinal bloodvessels was noted. No lymphatic enlargement. Liver was the seat of a marked coccidiosis. Cultures from the blood, liver, spleen, intestinal wall, urine and feces were all negative for Bacillus typhosus; those from the gall-bladder wall and bile were positive.

No. 3. Weight, 1895 grams. Vaccinated. Blood and feces were examined December 30, January 1, 8, 10, 14, 22, 31, February 7, 14, 16, 19, 20. Blood contained Bacillus typhosus until February 3, and the feces until February 8; twenty-five and thirty days respectively. Vaccinated February 8 with 10,000,000 organisms, repeated on February 10 with a dose of 20,000,000. Agglutinins, January 8, 1 to 200; February 16, 1 to 400. This animal lost weight rapidly from the time inoculated. On February 14 a peculiar swaying motion of the head and slight twitching of the hind legs were noted. These symptoms increased in severity, the animal growing progressively weaker until death ensued February 21; weight, 1100 grams; loss, 795 grams. No lymphatic enlargement or vascular engorgement noted. Liver was large and fatty. Gall-bladder contained 1 c.c. of a pale, straw-colored fluid in which were numerous flocculi. Gall-bladder wall was necrotic in places. The skull cavity was opened, no excess of cerebrospinal fluid found, or evidence of pus. Cerebral bloodvessels were engorged throughout. Brain substance was exceedingly soft. Cultures from the gall-bladder wall, the brain cortex, and brain tissue on section gave positive results culturally for Bacillus typhosus. The urine, blood, feces, intestinal wall, and bile were all negative.

No. 4. Weight, 1125 grams. Unvaccinated. Blood and feces examined December 30, January 1, 8, 11. Both contained Bacillus typhosus on the above dates. Agglutinins, January 8, 1 to 100. Died January 14, weight 920 grams; a loss of 205 grams. At necropsy no vascular engorgement or lymphatic enlargement noted. The liver was the seat of marked coccidiosis. The gall-bladder was small and contracted. Bacillus typhosus was recovered from the gall-bladder wall.

No. 5. Weight, 1050 grams. Unvaccinated. Blood and feces examined December 30, January 1, 8, 10, 14, 16, 19, March 7, 16,

25. Blood contained Bacillus typhosus from January 1 to February 3, and feces until March 25; thirty-four and eighty-five days respectively. Agglutinins, January 8, 1 to 400; February 8, 1 to 400; February 29, 1 to 200; March 20, 1 to 100. Killed March 28; weight, 700 grams, a loss of 350 grams. The gall-bladder was small and contracted, containing 0.3 c.c. of a pale yellowish-green, curdy fluid. The wall was thickened and necrotic in places. Bacillus typhosus was recovered from the gall-bladder wall. Sections of the gall-bladder wall, examined microscopically, failed to show any organisms.

THIRD SERIES

All of the animals of this series were inoculated January 11, 1912.

No. 1. Died within an hour following inoculation. At autopsy an embolus of one of the arteries at the base of the brain was found. Blood cultures were negative.

No. 2. Weight, 1420 grams. Vaccinated. Blood and feces examined January 17, 28, February 14, 16, 19, 21, 23, 24, 25, 26, 27, 28, March 5, 7, 16, 25, April 3, 10. Blood contained Bacillus typhosus from January 17 to February 27; and the feces until February 28; forty-one and forty-two days respectively. Agglutinins, January 18, 1 to 100; January 26, 1 to 200; March 16, 1 to 100. Operated on February 17; gall-bladder aspirated. Fluid was plated out and found to contain Bacillus typhosus. Vaccinated February 20, March 4, and April 3, with 20,000,000 organisms at each treatment. Died April 23; weight, 1100 grams; loss in weight of 320 grams. Gall-bladder contained 0.5 c.c. of a thin straw-colored fluid. The gall-bladder wall was normal. Cultures of blood, spleen, bile, gall-bladder wall, and feces were all negative for Bacillus typhosus.

No. 3. Weight, 980 grams. Unvaccinated. Blood and feces examined January 17, 28. Both blood and feces contained Bacillus typhosus on the above dates. Agglutinins, January 18, 1 to 100. Died February 3, weight, 750 grams, a loss of 230 grams. Coccidiosis of liver was found at autopsy. Cultures from blood, liver, spleen, gall-bladder wall, bile, feces, and intestinal wall were all negative for Bacillus typhosus.

No. 4. Weight, 1450 grams. Vaccinated. Blood and feces examined January 17, 28, February 14, 16, 19, 21, 23, 24, 25, 26, 27, 28, March 5, 7, 10, 25, April 3, 10. Blood contained Bacillus typhosus from January 17 to February 16, and the feces until February 28; thirty and forty-two days respectively. Agglutinins, January 18, 1 to 200; January 26, 1 to 200; March 16, 1 to 300; April 20, 1 to 200; May 3, 1 to 100. Gall-bladder aspirated February 17; fluid gave positive results for Bacillus typhosus. Vaccinated with 20,000,000 organisms February 20 and April 3. Weight, May 4, 1230 grams, a loss in weight of 220 grams.

No. 5. Weight, 1210 grams. Vaccinated. Blood and feces examined January 17, 28, February 14, 16, 19, 21. Blood contained Bacillus typhosus until February 16; and feces until February 21; thirty and thirty-five days respectively. Agglutinins, January 18, 1 to 80. Vaccinated with 25,000,000 organisms February 20. Died February 22, weight, 1070 grams, a loss of 140 grams. The liver showed fatty change; gall-bladder was small, wall thickened and necrotic in places. Bile thick and dark brown in color. The blood, bile, gall-bladder wall, feces and urine were cultured; the bile, gall-bladder wall, and the feces gave positive results culturally for Bacillus typhosus.

No. 6. Weight, 1450 grams. Unvaccinated. Blood and feces examined January 17, 28; both were positive on these dates. Died February 8; weight, 1320 grams; loss in weight, 130 grams. Marked coccidiosis of liver. Bacillus typhosus recovered from gall-bladder wall.

No. 7. Weight, 1230 grams. Vaccinated. Blood and feces were examined January 17, 28, February 14, 16, 19, 22. Blood was negative on February 16, but contained Bacillus typhosus on February 19 and 22; feces contained Bacillus typhosus until February 16; thirty-six and thirty days respectively. Agglutinins, January 18, 1 to 80. Vaccinated with 20,000,000 organisms February 28. Died March 3, weight 800 grams, a loss of 430 grams. Nothing abnormal noted at the autopsy. All cultures were negative.

No. 8. Weight, 1000 grams. Vaccinated. Blood and feces examined January 17, 27, February 14, 20, 22, 28, March 5, 16, 25, April 10. Blood contained Bacillus typhosus until February 14,

and the feces until March 5; twenty-eight and forty-eight days respectively. Agglutinins, January 18, 1 to 200; February 20, 1 to 200; March 17, 1 to 300; April 30, 1 to 200; May 3, 1 to 100. Vaccinated with 20,000,000 organisms March 15 and April 30. Weight, May 4, 870 grams, a loss of 130 grams.

FOURTH SERIES

All animals were inoculated February 28, 1912.

No. 1. Weight, 1890 grams. Unvaccinated. Blood and feces were not examined. Died March 6, during a convulsion. The liver was found to be enlarged and pale in color. Gall-bladder was distended and contained 1.5 c.c. of a pale, yellowish fluid containing flocculi. Cultures from the liver, spleen, gall-bladder wall, and intestinal wall were all negative; those from the bile, blood, and feces were positive for Bacillus typhosus.

No. 2. Weight, 1550 grams. Vaccinated. Blood and feces examined March 7, 16, 25, April 10, 17, 19, May 1. Blood contained Bacillus typhosus from March 7 to April 10, and feces until April 19; thirty-four and forty-three days respectively. Vaccinated with 25,000,000 organisms April 10. Agglutinins, March 16, 1 to 200; March 28, 1 to 200; April 17, 1 to 300. Weight, May 4, 1210 grams, a loss of 340 grams.

No. 3. Weight, 1470 grams. Vaccinated. Blood and feces examined March 7, 16, 25, April 10, 17, 19, May 1. Blood contained Bacillus typhosus until April 10; and feces until April 17; thirty-four and forty-one days respectively. Vaccinated with 25,000,000 organisms April 10 and May 4. Agglutinins, March 16, 1 to 200; March 28, 1 to 200; April 17, 1 to 400. Weight, May 4, 1180 grams, a loss of 290 grams.

No. 4. Weight, 1250 grams. Unvaccinated. Blood and feces examined March 7, 16, 25, April 10, 17, 19, May 1. Blood contained Bacillus typhosus until April 17, and the feces until May 1; forty-one and fifty-six days respectively. Agglutinins, March 16, 1 to 200; April 17, 1 to 200. Weight, May 4, 1180 grams, a loss of 70 grams.

No. 5. Weight, 1130 grams. Unvaccinated. Blood and feces were examined March 7, 16, 25, April 10, 17, 19, May 1. Agglu-

tinins, March 16, 1 to 200. Blood contained Bacillus typhosus until April 19; and feces still did so on May 1; forty-three and fifty-two days respectively. Weight, May 4, 1270 grams, a gain of 140 grams.

No. 6. Weight, 1240 grams. Unvaccinated. Blood and feces were examined March 7, 16, 25, April 10, 17, 19, May 1. Agglutinins, March 16, 1 to 200. Blood contained Bacillus typhosus until April 10; and feces still did so on May 1; thirty-four and fifty-five days respectively. Died May 1, weight, 1180 grams, a loss of 60 grams. Liver was larger than normal, with a few small, pale yellowish areas scattered over the surface. These areas varied in size from 1 to 3 mm. in diameter. On section small abscesses were revealed. The pus in the miliary abscesses in the liver and that in the gall-bladder yielded pure cultures of an organism that was identified as Bacillus coli verus. Typhoid bacilli were recovered from the feces.

No. 7. Weight, 1170 grams. Vaccinated. Blood and feces were examined March 7, 16, 25, April 10, 17, 19, May 1. Blood contained Bacillus typhosus until April 10; and feces until April 20; thirty-four and forty-four days respectively. Agglutinins, March 16, 1 to 200; March 28, 1 to 200; April 28, 1 to 400. Vaccinated with 25,000,000 organisms April 10. Weight, May 4, 1170 grams.

The opsonic index was determined, using Wright's method; the pooled sera from three uninoculated rabbits being used as a control. The index was high, running from 1.6 to 3.2, thus bearing a close relation to the human chronic carrier as reported by Stone.[9] Following vaccination the opsonins were increased, the average of all vaccinated animals being 4.7. Counts of the erythrocytes and differential counts of the leukocytes were made; the differences from the normal rabbit's blood as determined by Brinckerhoff[12] were so slight as to add no evidence of value. The bacteriolytic and bactericidal properties of the sera of the vaccinated animals were found to be increased; whereas in the controls (unvaccinated rabbits) the above properties were practically non-existent, thus agreeing very markedly with Stone's findings in human carriers recently reported.[9]

SUMMARY

The organisms began to appear in the blood and feces in from seven to ten days after inoculation except in two instances, these animals developing a diarrhea and Bacillus typhosus being recovered on the third day. In the vaccinated animals the organisms disappeared from the blood in from about thirty-five to forty-five days after inoculation; from the feces in from about forty to fifty-five days. Animals were vaccinated in from thirty-six to forty-eight days after inoculation. In the unvaccinated rabbits the typhoid bacilli disappeared from the blood in from about thirty to sixty days after inoculation; from the feces in from sixty to one hundred and ten days. Seven vaccinated animals came to autopsy from forty-two to one hundred and six days after inoculation; from two to sixty-three days after vaccination. Five were negative culturally for Bacillus typhosus; 2 were positive. One of these died two days after vaccination; the other died with symptoms of meningitis thirteen days after vaccination. In the latter case Bacillus typhosus was recovered from the gall-bladder wall and the brain only. Eleven unvaccinated rabbits were examined post mortem from seven to one hundred and twenty-seven days after inoculation; but one gave negative results for Bacillus typhosus culturally. Seven showed Bacillus typhosus in the gall-bladder wall only; of these 5 had been negative culturally prior to death; 1 dying seven days after inoculation, showed the bacilli in the bile, blood, and feces only; 1 dying sixty-three days after inoculation showed the bacilli in the feces only; Bacillus coli verus was found also.

The gall-bladders of 2 animals of the third series (blood and feces negative) were aspirated about thirty days after inoculation; the bile contained Bacillus typhosus, when examined culturally. Both animals were vaccinated three days later. One died sixty-three days after vaccination; results culturally were negative. The other is still alive and apparently in good health. After the disappearance of the organisms from the feces of the controls of the first series, 2 of these rabbits (unvaccinated) were given repeated doses of eserine and pilocarpin, with the hope of starting up a catarrhal condition in the gall-bladder and causing any retained organisms

to again enter the intestinal tract. This treatment was of no effect; so 15 c.c. of beef bile were then introduced into the stomach of one rabbit. A marked diarrhea ensued and death in about six hours. At the autopsy the whole intestinal tract was found to be hyperemic; the bloodvessels of the gall-bladder wall were engorged. Bacillus typhosus was recovered from the gall-bladder wall and the feces. A second control was given beef bile in doses of 1 c.c. until diarrhea was produced. Feces contained Bacillus typhosus. This animal was killed and Bacillus typhosus recovered from the gall-bladder wall and the feces.

CONCLUSIONS

1. The condition analogous to the typhoid carrier state in man can be produced in the rabbit.

2. Bacillus typhosus can be recovered from the blood up to the end of the first month and longer following inoculation, and from the feces up to one hundred and ten days.

3. Bacillus typhosus can be recovered from the bile approximately from thirty to sixty days after inoculation, and would then seem to become attached to the gall-bladder wall, since postmortem examination revealed the presence of Bacillus typhosus in the gall-bladders of 9 of 11 unvaccinated animals examined; and no Bacillus typhosus could be found in the gall-bladders of 5 vaccinated animals so examined.

4. An inoculated animal becoming a carrier may have a reappearance of the typhoid organisms in the feces due to a catarrhal condition affecting the gall-bladder.

5. From the results obtained in this experiment, vaccination would certainly seem to be indicated as a means of treatment in the human carrier, and also as a prophylactic agent in the prevention of such carriers.

6. A routine examination of the stools and urine of all typhoid convalescents should be required by municipal health authorities until successive cultures are negative,[13] as is at present the practice with cases of diphtheria.

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HOSPITALS AND TYPHOID CARRIERS

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During the last two years an increasing amount of attention has been called to the danger to the public health of typhoid carriers, and to the importance of their recognition and control. In August of last year, Meakins, of Montreal, in an exhaustive article on the subject, urged that in our general hospitals, where at least 50 per cent. of the cases of typhoid fever are treated, every case of the disease should be examined bacteriologically during convalescence, and should be kept in the hospital or under strict observation and be treated by homologous vaccines until the excreta were free of typhoid bacilli. Meakins further advised that patients under the care of physicians in private practice should be watched and examined from time to time by officials of the board of health. Impressed by the suggestion of the Canadian writer, I requested Dr. Norris, the director of laboratories in Bellevue and its allied hospitals, to have the feces and urine of all cases of typhoid fever examined during convalescence. This work was begun in September, 1911, and has continued up to the present time. One hundred and nineteen cases in all have been examined, and of these 15, or 12.6 per cent., had typhoid bacilli in either the feces or the urine or in both. An average of two examinations was made in each case. Forty-eight cases were also examined during the active stage, with a positive result in 10, or in 20.83 per cent. From these figures it appears that about 1 case in 5 gave positive findings during the active stage of the disease, but only 1 in 8 cases by the time they had arrived at convalescence. All patients with the exception of two were bacteriologically free

before they left the hospital. These two patients were discharged inadvertently. Their names and addresses and occupations were sent to the Board of Health, though not as promptly as might be wished, as the mistake was not discovered for some time. Our own social service department is also endeavoring to trace them in order that we may make further examinations, if possible, and determine if they are still carriers. At present, no typhoid patient is discharged from any of the hospitals in the department except with the approval of the general medical superintendent. We have found no great difficulty in holding patients until they are presumably bacteria-free, at least two successive negative examinations being required in every case.

It may be urged that patients discharged as bacteria-free after only two examinations with negative results are still potential carriers and would prove to be actually such on further examination. It is believed, however, that this measure of precaution will serve to arrest the great majority. As the work progresses and our methods improve with experience, we shall no doubt be able to increase the number of examinations, at least in those cases that have given positive results at some time in the course of the disease. Dr. Norris is trying to devise some method of securing the bile which may enable us to arrive at more exact conclusions. Dr. William Hallock Park has also some such procedure in view. As he is here today perhaps he will tell us how far he has progressed in his plans.

There is one measure at least that we can take to guard the public health against infection by typhoid carriers either actual or potential, and that is to instruct them in the simple rules of cleanliness. This we should do with all cases of typhoid fever when they leave the hospital or pass from our observation in private practice, but particularly should we do this in the case of those who have shown themselves to be at least transitory carriers. Those who are engaged in the preparation or distribution of food should be doubly warned in this regard. We are now preparing a leaflet of instructions to be given to each patient on discharge from the hospital. It would be well, of course, to prevent such persons from following occupations involving the handling of food

or drink, but this in many instances would probably be impossible, particularly in this country. At all events, this is the province of the Board of Health, not of the hospital. It is for us to instruct the patient and give notice to the health authorities, that they may take the necessary measures to protect the public. It may be of interest to note the proportion of those engaged in occupations in which they were liable to infect others. In the hundred and forty different individuals who form the subject of this study there were fourteen housewives, three nurses, three waiters, two cooks, one orderly, one butler, and one baker, twenty-five in all. One has but to read this list to see how impossible it would be to compel any considerable number to change their occupation. Hence the importance of instructing them both orally and in writing how to avoid conveying infection.

Regulations for the control of typhoid carriers have been enforced in some countries of Europe for a number of years. In the south-western provinces of Germany there is probably no case of typhoid fever released from observation until the bacteriologic examination of the feces and urine has proved negative. In England, also, typhoid carriers receive a great deal of attention, especially in the English army. After treatment for a period of three months, if it is found that the soldiers are still carriers, they are given the opportunity of entering the hospital or of being discharged. In case of discharge, notification is sent to the medical officer of health of the district in which the soldier is going to reside. In the service in India two convalescent depots were established several years ago, to which the convalescents of certain military stations are sent. After the opening of these depots, namely, Wellington and Naini Tal, it was found that the admissions of typhoid fever from all stations which sent their convalescents there show a reduction of 9 per cent. in 1908 from the figures for the previous year, whereas the remaining stations show an increase of 26.6 per cent.

In the endeavor to sterilize typhoid carriers various methods of treatment have been tried, such as the use of lactic acid bacilli, acidifying the urine, the administration of antiseptics, the use of the *x*-ray, and the employment of vaccine. The surgeons of the English army report the following results of the use of these

five different means of treatment: (1) Lactic acid bacilli cause only a temporary disappearance of the typhoid bacilli. (2) Acidifying the urine fails to cure typhoid bacilluria. (3) The administration of antiseptics invariably brings about a decided diminution in the number of bacilli both in fecal and in urinary carriers. This effect is much more marked when the maximum contact of the antiseptics with the bacilli is obtained by combining the treatment with low diet and aperients in the case of "fecal," and with diuretics in the case of "urinary" carriers. (4) The use of *x*-rays in the cases of gall-bladder infection seems to have definite beneficial results. (5) Vaccines, like the lactic acid bacilli, cause only temporary disappearance of typhoid bacilli. It is suggested that the treatment by vaccines might have a better chance of success if combined with diuretics in the case of "urinary" carriers, and with *x*-ray treatment in gall-bladder cases. Sir Almroth Wright has pointed out that a vaccine is more likely to be efficient when the local conditions are so altered as to permit the fullest possible contact between the bacteriolytic products in the blood and the bacteria involved.

Other observers have had better results with vaccines than the English army surgeons. Some have reported permanent cures in cases of long standing, notably Meakins, in 2 cases described in detail, one of chronic bacilluria of twelve years' duration, the other one of chronic suppurative cholecystitis with gallstones of eight years' duration. At Bellevue we have as yet had to do only with transitory carriers, but Dr. Norris is prepared to use autogenous vaccination when occasion arises.

In conclusion, I am glad to add that these investigations have not proved burdensome to our pathological department, nor have they interfered with the regular routine of the laboratory. The clinical side of the problem presents somewhat greater difficulties, as we have to deal with the changing house staffs of four different hospitals, and it is not always easy to secure their effective coöperation. Gradually, however, even these difficulties are being overcome and we may reasonably expect that with patience and persistence and good-will on all sides they will give us less and less trouble in the future.

DISCUSSION

Dr. William H. Welch: I should like to say a word about those old experiments of Lockett's to which Dr. Abbott referred. It was almost an accident that we made the discovery. We found by inoculating intravenously certain doses killed. Other doses produced no effect at all. The animals were preserved, and one of them died three months afterward, and we made this observation which attracted our attention, and we found that these doses short of the fatal gave varying effects. I had the impression that only a certain percentage of those which were unaffected by the intravenous effect of the typhoid bacillus on account of the smallness of the dose and the virulence of the infection developed this biliary infection. We usually found in these cases small focal necrosis in the liver. I have no doubt that we should find that the cells were the cells which picked the typhoid out from the circulation, and it is from these cells with their peculiar eliminative activity that the typhoid bacilli get into the bowel. These bacilli become carriers. This work was done twenty years ago. The changes in the bile were interesting. It lost a good deal of its coloring matter, it was watery, and there was grumous matter, and this led us to make the examination which resulted in finding the bacteria. My impression is that it is, on the whole, exceptional rather than the rule that the typhoid bacilli injected into the veins of rabbits establish themselves permanently in the gall-bladder, but once established there can certainly survive almost indefinitely. It is well known there was for a time an impression that they were the carriers from biliary infection. My impression is that the idea that any large percentage of carriers are carriers by virtue of the presence of the typhoid bacilli in the gall-bladder rests on a rather weak basis. The gall-bladder has been removed in some of these carriers and in some instances it resulted in the removal of the typhoid bacilli altogether in the stools. In other cases it has been entirely unsuccessful, so I do not suppose we are justified in supposing they are typhoid carriers solely because of their biliary infection. It is curious to me, on the whole, that vaccine with the quick culture should influence the typhoid bacilli in the bile. I understood Dr. Abbott to say that he found bacilli in the bile. I understood Dr. Abbott to say that he found the typhoid bacilli in the blood in forty days. In our cases the typhoid bacilli disappeared from all the organs of the body except the bile within a week or so. Of course in the bile, necessarily in the stool.

Dr. William H. Park: I think Dr. Brannan's plan is a good one. Five years ago we examined a large number of stools from convalescent typhoid cases. The health department found it almost impossible to take care of the half-dozen carriers found. I think if we get knowledge of

these cases and instruct them as to their conditions, we have done all that is possible. It is well worth while doing this, and perhaps later more can be attempted and accomplished.

Major Frederick F. Fussell: The vaccination of carriers we know is not always successful. I have had one carrier under observation for two and one-half years, and he has been vaccinated with stock and autogenous vaccines for fully two years without any effect upon his bacilli. At times as many as 90 per cent. of the living bacteria in his stools are typhoid; the percentage averaging somewhere between 30 and 90. Perhaps one examination out of ten will be negative for typhoid bacilli. He has no biliary symptoms, in fact, no symptoms of any kind, and denies having had typhoid. In regard to instruction in personal cleanliness, we have had a great deal of experience in instructing soldiers in cleanliness both in field and in barracks, and it is very uphill work. We find they are really too old to be taught personal cleanliness. That has led me to inquire as to what was done in public schools; whether the children could wash their hands after going to the toilet if they wished to, or not. I find in most schools they cannot. After they grow up they are too old to teach. We fail, at the present time, to teach personal cleanliness in the public schools while the children are still of impressionable age.

WEIGHT-CURVES IN TYPHOID FEVER

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While there can be little doubt that under the ancient doctrine of "stuff a cold and starve a fever" loss of weight in the continued fevers was even greater than it is today, I shall confine the present discussion to the period during which typhoid fever has been recognized as a distinct disease, that is, since 1837, when Gerhard and Pennock finally established its differentiation from typhus fever. From that time to the present emaciation has been considered a characteristic symptom of the disease. It occurs in greater or less degree in all or nearly all cases. It is prominently mentioned in all complete descriptions of the disease and has been regarded as a deplorable but necessary consequence of the infection. According to Loomis: "Emaciation is perhaps more marked and rapid in this than in any other form of fever. It commences early and is progressive. By the time a patient has reached the fourth week of a typhoid of even moderate severity, he is usually in a condition of extreme emaciation." On the other hand, while admitting the occurrence of extreme grades of emaciation, Curschmann thinks that the losses in typhoid fever are not so great as would be anticipated, if one considers the duration of the disease and the extent of the losses in other infections.

Comparatively early in the history of typhoid fever exact observations were made upon the extent of the loss in weight. Yet in view of the fact that the majority of authors do not record the amount of food taken, it is difficult to compare their results. In a few instances, however, they have either platted out the weight curves or have furnished data from which such curves could be constructed.

The following general summary represents, I believe, the most important results of all previous investigations:

Loss of weight occurs in practically all cases of typhoid fever, but varies greatly in extent.

The severer the infection and the longer the duration of the disease, the greater the total loss.

The greatest loss observed by Curschmann at the beginning of convalescence was 41 per cent. of the body weight. Scharlau had previously recorded a loss of 30 per cent. Losses of 19 per cent. in severe and of 10 per cent. in mild cases are common (Curschmann). On the other hand, the losses may be relatively insignificant, 1.5 per cent. to 3 per cent. in severe and 1 per cent. to 1.1 per cent. in mild cases (Curschmann).

Daily losses of 300 to 500 grams are common; they may reach 1500 grams (Botkin); and in a case complicated by parotiditis the loss amounted to 2500 grams in one day (Lorain).

Lorain states that the maximum loss is reached at the end of the second or beginning of the third week, while according to Curschmann it is reached more frequently in the third than in the second week.

Kohlschütter found that, after the more active period of the disease is over, the losses diminish with each week up to complete defervescence. Puritz observed a corresponding diminution in the elimination of nitrogen.

Complications increase the loss of weight (Lorain, Cohin).

While loss of weight usually ends with the return of the temperature to normal, it may extend far into convalescence (Leyden), according to Curschmann to the third week. Curschmann has observed a loss of four pounds in the first week of convalescence.

All patients gain weight in convalescence, some rapidly, apparently without much, if any, increase in the quantity of food.

Contrary to the conclusions of the majority of observers, Garnier and Sabaréanu found in their cases that the weight remained stationary, or increased a little, during the active febrile period; it diminished rapidly at defervescence; and in the afebrile period, remained unchanged until the patient began to take more food,

when it increased. They attribute the course of the curve to the retention of water and its sudden elimination.

Figs. 1 and 2 are taken from Puritz and Lorain. They illustrate the main features of the summary. Puritz's patient received a relatively full diet, taking an average of 160 grams of protein, 60 to 90 grams of fat, and 300 grams of carbohydrate a day. Lorain's patient received only a few spoonsful of milk.

The loss of weight in typhoid fever has been attributed to three factors: 1. Partial starvation. 2. The febrile temperature. 3. The toxic destruction of protein.

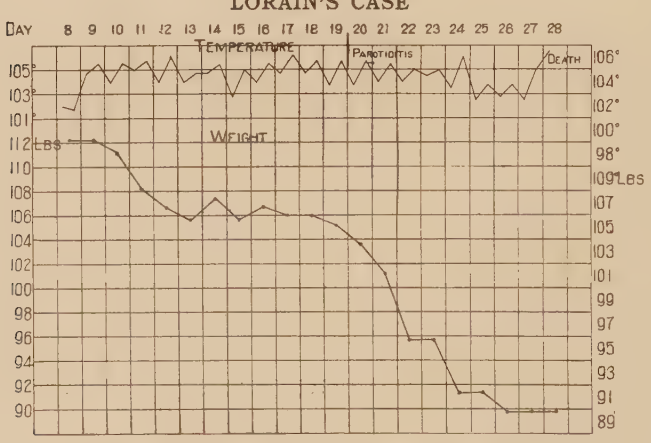

FIG. 1.—Showing influence of complication on weight. Patient received only a few spoonsful of milk a day.

1. *Partial Starvation.* Apparently at all periods in the history of typhoid fever it has been recognized that patients suffering from the disease were undernourished. Bretonneau characterized their condition by the term *autophagia*. Graves, Trousseau, Tschudnowsky, Flint, Barrs, and Shattuck insisted, in their respective periods, that typhoid fever patients were undernourished, and introduced diets of greater nutritive value.

Proof of the influence of partial starvation upon the loss of weight occurring during the disease is furnished by the observations of Puritz, von Leyden and Klemperer, and others who succeeded in

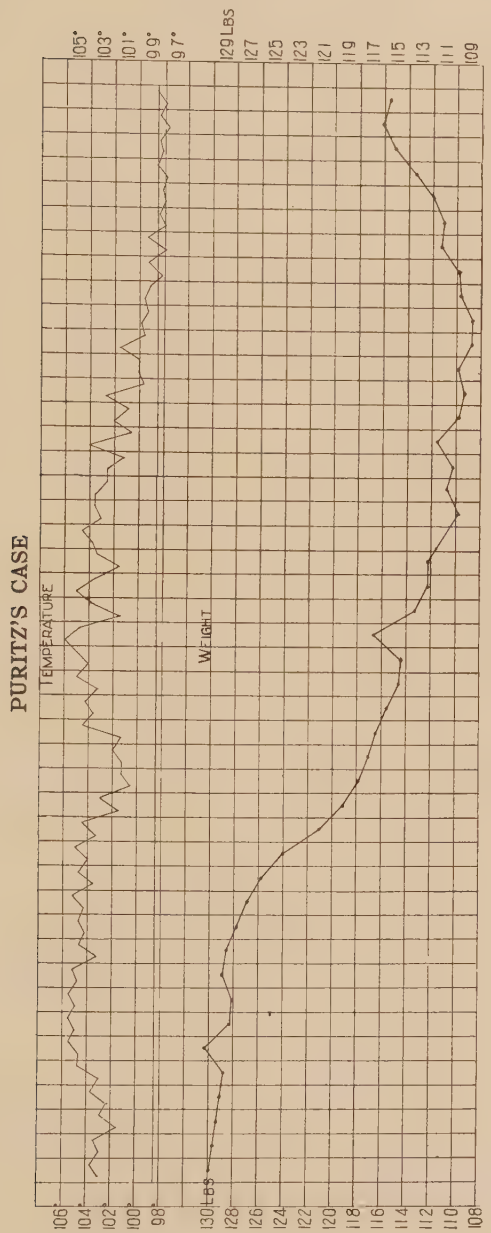

FIG. 2.—Patient received an average of 2600 calories a day.

diminishing the loss by increasing the intake of food. Recently it has been found possible to maintain many patients in weight equilibrium by administering sufficient food.

2. *The Febrile Temperature.* The effects of an artificially raised temperature (through hot baths, heated air, or injury to the heat centres) upon protein metabolism are comparatively well known. It is probable, but has not been proved, that fat and carbohydrate metabolism are similarly affected. Temperatures under 39° C. cause only slight increase in protein destruction; temperatures over 39° C. likewise have but little effect unless they are prolonged for more than three hours; artificial heating for twelve hours has caused an increase in protein destruction amounting to 37 per cent. (F. Voit).

These results apparently confirm the clinical observation that intermittent temperatures are not, as a rule, attended by such marked loss of weight as those which are continuous. They also suggest that the diminished loss in the later stages of typhoid fever may be due in part to the change in the character of the temperature curve.

3. *Toxic Destruction of Protein.* The loss of nitrogen in the infective fevers is greater than occurs in a healthy man who is starved, or, according to common belief, than can be accounted for by the pyrexia itself. Upon this basis it has been assumed that the toxins of the infecting microörganism exert directly a destructive influence upon the cells of the body.

Whether the theory, in its generally accepted form, is correct or not does not concern us at this time. It has been proved possible to bring a patient suffering from typhoid fever into nitrogen and weight equilibrium by the exhibition of a diet containing a large amount of carbohydrate and a relatively small amount of protein.

Water-retention Theory. The discussion of weight-curves in typhoid fever would not be complete without reference to the theory of water retention. This theory must be considered from two standpoints: (1) The influence of the disease itself, and (2) the influence of a diet containing a large amount of carbohydrate.

1. *The Influence of the Disease.* The water balance has not been thoroughly investigated for any fever, and conflicting opinions are held concerning it in typhoid fever.

Leyden was one of the first to refer to the theory of water retention. The sudden losses of weight which have been observed with remissions of temperature, especially toward the end of the febrile period, probably indicate that water is retained in some cases. Yet Krauss speaks of the "alleged retention of water in fever," as pure "conjecture," Stähelin's dog, infected with surra, eliminated more water than he ingested. Schwenkenbecher and Inagaki conclude from their experiments that water is not retained in the body in fever.

On the other hand, Garnier and Sabaréanu believe that retention of water occurs during the febrile state of typhoid fever and that this is responsible for the supposed maintenance of weight during this period.

In view of the conflicting opinions and the absence of conclusive studies of the water balance, the question of water retention in fever, due to the disease itself, must be left open for the present.

2. *The Influence of a Diet Rich in Carbohydrate.* The increasing use of diets rich in carbohydrate in typhoid fever renders it important to determine whether such a diet is likely to cause retention of water in the body. As is well known, a poorly balanced diet may cause variations in the excretion of water. For example, in an experiment conducted by Benedict and Milner, it was found that water was retained on the first of three days when the subject was confined to a diet consisting of 965 to 969 grams of carbohydrate; on a diet of 745 to 750 grams of fat, water was lost during the whole period. It is generally agreed, however, that a well-proportioned diet does not affect the water balance.

While the proportions of the foodstuffs in the diet which we employ varies necessarily with different patients, and in some instances have been subject to sudden experimental changes, there has been no constant relation between variation in weight and the quantity of urine. Though water may have been retained by some patients, and have caused an increase in weight, there has been no clinical reason to think that such was the case. There

has been no visible edema, and patients have not lost weight suddenly, following diuresis, when the amount of carbohydrate in the diet was diminished during convalescence.

In addition to the above considerations, we now possess evidence that at least a part of the gain in weight in the late stage of the febrile period and in convalescence is due to the conversion of dextrose into fat. In one instance, 38 per cent. of the carbohydrate metabolized during the period of observation (15 minutes) was so transformed.[1]

The *distribution* of *the losses* among the various tissues of the body requires brief consideration.

It appears probable that all of the tissues share in the losses, though to what relative extents can only be surmised at present. The increased elimination of nitrogen in patients who are undernourished forms the basis for the assumption that the muscles suffer marked loss. Loss of fat, as well as of muscle, is evident clinically in severe cases.

With the aid of a respiration chamber, Grafe studied the respiratory quotients of typhoid fever patients in the fasting state, and reached the conclusion that the metabolic processes follow normal laws, though with increased intensity. Rolly's studies on the respiratory quotients of patients from four to six hours after food, and our own studies in Bellevue Hospital upon patients taking a full diet, lead to the same conclusion. If these results are ultimately confirmed, the consumption of the body tissues in typhoid fever, when the patients are undernourished, proceeds in the same manner as in healthy persons who are partially or completely starved. The stores of glycogen are depleted first—probably within a few hours when the fever is high and, at most, within a few days—after which fat and protein constitute the sole sources of the body's energy. The duration of life in a healthy animal which is starved is measured by the amount of fat which the body contained at the start (Lusk). The often noted fact that obese patients do not bear typhoid fever well does not come into consideration here, since the causes of this fact can only be

[1] Unpublished observations upon the respiratory exchanges carried out with the assistance of Dr. E. F. Du Bois.

conjectured. Another analogy of the processes of metabolism in typhoid fever to those in starvation must be noted; in partial or complete starvation the body begins, after a time, to economize its available energy by reducing its total metabolism. A similar economy of energy has frequently been observed in typhoid fever. Moos found as long ago as 1855 that the nitrogen losses diminished in the later weeks of the disease. Kohlschütter emphasized his observations that the loss of weight diminishes with each week after the more active period of the disease is past. Cohin called attention to the same fact. This is the probable explanation of the continuance of life in patients who take a wholly inadequate amount of food and yet live from week to week with high fever.

My own observations upon the weight curve in typhoid fever were begun in 1908. A satisfactory balance could not be obtained upon the market, so I had the hospital carpenter construct a wooden table which would rest upon the platform of the ordinary hospital scales. When in position the table is the same height as the bed, and the weight of a patient may be taken without more disturbance than shifting his position in bed—with much less exertion, in fact, than is required to administer a tub bath.

Weights have been taken of practically all patients, usually every second or third day. The procedure was adopted originally for the purpose of having additional clinical control upon the effects of the diet. Slight sources of error enter into the observations, which are clearly recognized, but which so far it has been impossible to eliminate.[1] While such errors may, and probably do, affect the relation of one day's weight to another, apparently they do not affect the general trend of the curve. The errors referred to are: Patients have not always been weighed at the same hour of the day or with regard to whether they have recently been fed or have urinated. The morning defecations do not come into consideration as the weights have never been taken before the administration of the daily enema. The clothing of the patients, however, has always been carefully considered. In future observations it is hoped that these sources of error may be eliminated.

[1] The weights have been taken by various members of the interne staff after the general demands of the wards have been attended to.

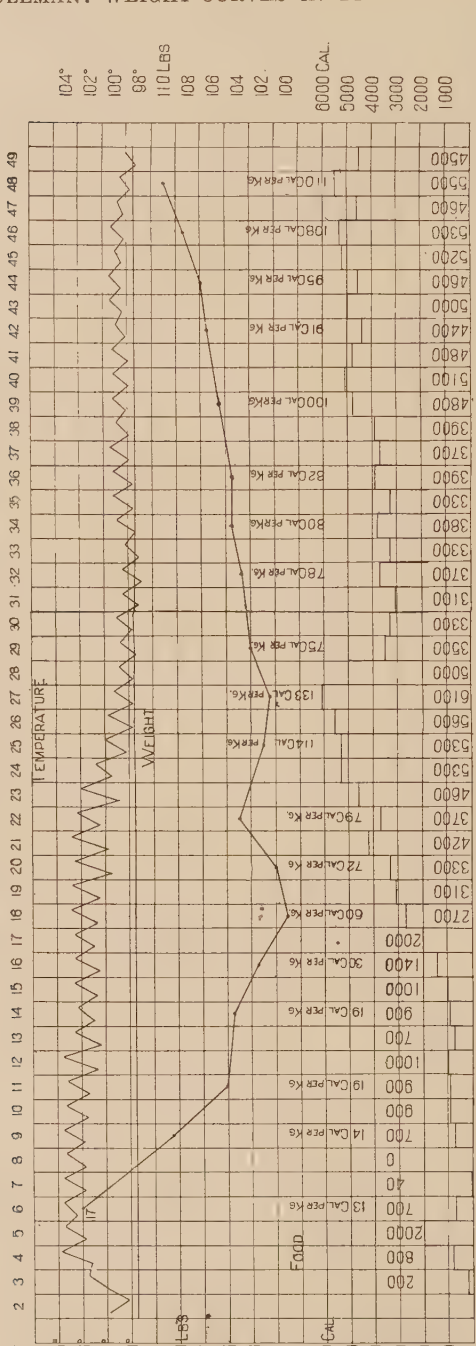

Fig. 3.—One of the earlier Bellevue Hospital cases, showing rapid loss of weight during the febrile period, when the amount of food was insufficient, and the gain in weight in convalescence.

The figures which follow, with the exception of Fig. 3, illustrate the influence of a full diet upon the weights of patients during the febrile period, convalescence, and relapses. The curves are typical

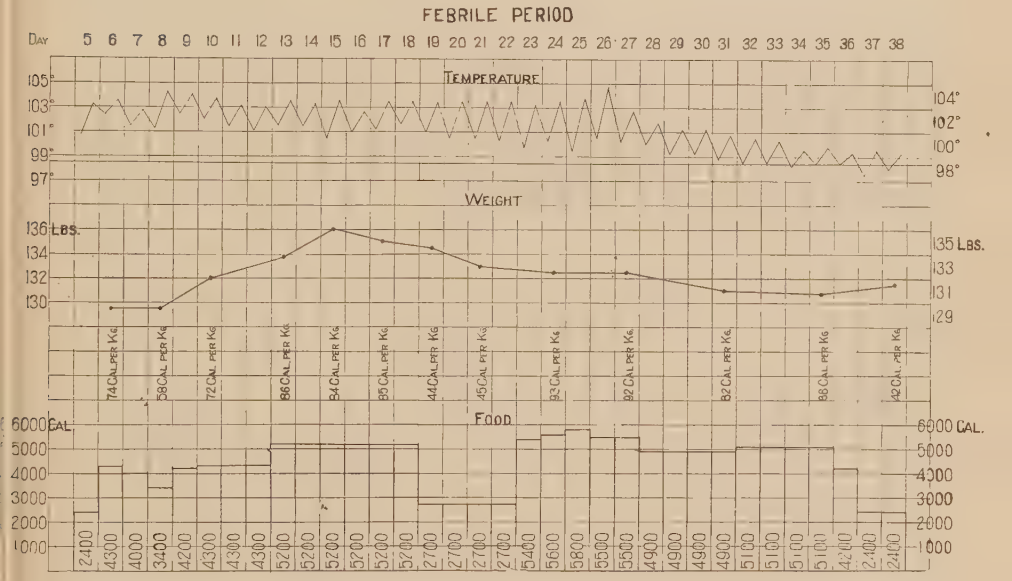

Fig. 4.—Showing that weight equilibrium may be maintained by sufficient food.

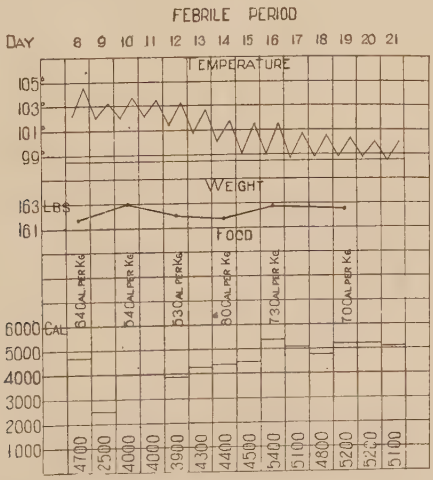

Fig. 5.—Showing the maintenance of weight equilibrium.

of the effects of the diet. Fig. 3 is the curve of one of the earlier patients of the series, to whom it was impossible, with our then limited experience, to give the amount of food required until toward the end of the febrile stage. The general course of the curve is similar to those obtained by the earlier investigators. There is no evidence in the curve of water retention either during the febrile period or in convalescence.

The gains in weight during relapses and in convalescence are less noteworthy than the maintenance of weight during the active stages of the fever.

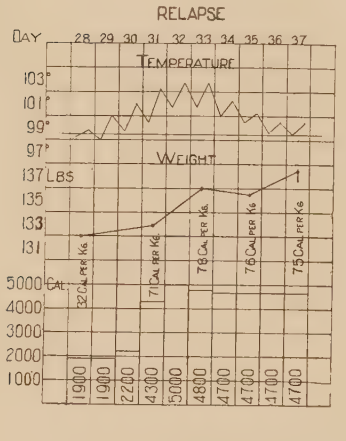

Fig. 6.—Showing an increase in weight during a relapse.

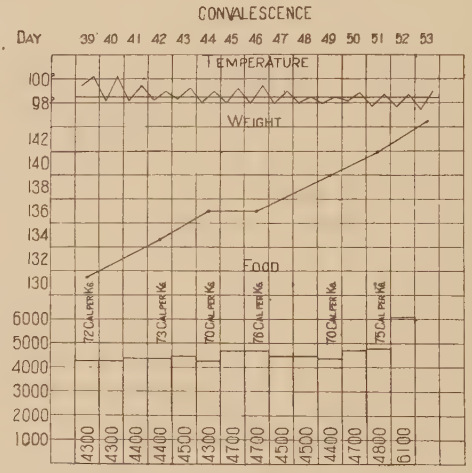

Fig. 7.—Showing rapid gain in weight during convalescence.

The ability of the body to repair its losses after wasting diseases is nowhere better shown than in convalescence from typhoid fever. This fact has been known for many years. Botkin stated that such patients gained weight rapidly at first, more slowly later. According to Liebermeister, patients may gain as much as five to seven pounds a week; according to Schottmüller, as much as eleven pounds. In Puritz's cases, the weight remained stationary for the first two or three days after the temperature reached normal and then began to increase. Fr. Müller found that patients convalescing from typhoid fever are able to retain nitrogen on a diet which, with its low fuel value, is insufficient to maintain nitrogen

equilibrium in health. He reports a case which retained from the third to the tenth day of convalescence a daily average of 1.3 grams nitrogen on a diet furnishing only 1165 calories and 9.9 grams of food nitrogen.

As is illustrated in Fig. 3, patients who have lost much weight during the febrile stage may repair the damage before they are able to get out of bed.

In one of Puritz's cases the weight remained stationary during a relapse of sixteen days' duration.

Conclusion. It is possible to maintain patients suffering from typhoid fever in weight equilibrium throughout the entire course of the disease by giving them sufficient food.

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DISCUSSION

Dr. Henry Sewall: Was there any peculiarity in the clinical course of these cases? Were they shorter or longer than normal?

Dr. Coleman: No.

ROYAL SOCIETY OF MEDICINE
26 MAR 1913

A CASE OF MENINGOCOCCUS ENDOCARDITIS AND SEPTICEMIA WITH LATE APPEARANCE OF MENINGEAL SYMPTOMS

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Cases of meningococcus infection involving primarily tissues other than the meninges are sufficiently uncommon to warrant the recording of the following case:

J. M., male, age forty-seven years, commercial traveller, was admitted to the Montreal General Hospital on March 12, 1912, complaining of palpitation and tightness across the chest and abdomen, cough, and expectoration.

As a child he had growing pains, and a few years ago suffered from sore throats. There was no history of rheumatism or venereal disease. He has been a heavy smoker and a free and steady drinker. Married and has had eight healthy children; wife has had no miscarriages. He has lived in this vicinity for twenty years.

His present illness began three weeks ago with chilly sensations followed by flushing and sweating. There was also a sharp stabbing pain in the right shoulder lasting an hour and leaving the joint painful and tender. Two days later he had a similar attack of pain in the left shoulder, while the right side gradually improved. In addition to these articular manifestations he had several slight attacks of pain over the heart, palpitation, shortness of breath on climbing stairs, and smothering sensations when lying in bed. There was some cough and expectoration; frequency of micturition,

three or four times at night; also chilly sensations followed by sweats. He had lost 20 pounds in weight.

Present Condition. The patient is a moderately nourished man, the face slightly flushed and the skin moist. Mentally he is bright and clear. No glandular enlargements. Temperature, 101$\frac{1}{5}$° F.; pulse, 88; good volume, blood pressure, 95; the arteries are not thickened. The cardiac impulse is not felt either in the sitting or lying posture; relative dulness begins at the third rib and extends to the nipple line on the left, 9 cm. from midsternum and 4 cm. to the right at the fourth rib. A soft systolic murmur is present at the apex. At the base a systolic murmur is heard at the pulmonary area with normal sounds at the aorta. The lungs present subcrepitant rales at the base behind, more extensive on the right than on the left side. The tongue is red at the tip and borders and thickly coated. The abdomen is somewhat distended; the liver is slightly enlarged, especially the left lobe; splenic dulness extends to the costal border and measures 15 cm. along the line of the ribs, but the organ is not palpable.

Urine. 1250 c.c. in twenty-four hours, acid, 1024, smoky, albuminous, no sugar, many red blood corpuscles and some leukocytes.

Diary. March 14. Orthopnea at night. Pain and swelling of the right middle knuckle-joint.

March 20. The temperature continues slightly elevated, from 98° to 101$\frac{3}{5}$° F., the urine continued smoky and albuminous, the specific gravity 1009 to 1020, once 1030, alkaline, with a few granular casts and many blood corpuscles. On March 20, Dr. Mathewson reported a retinitis in both eyes. A small quantity of fluid is present in the peritoneal cavity.

March 24. No special change in physical signs. Has complained at times of tightness across the chest; vomited a small quantity of fluid on two occasions; had a small epistaxis two days ago. Urine bloody. Temperature moderately elevated, maximum 101$\frac{3}{5}$° F.

March 26. He is very dull and soporose and on the following day, March 27, had a chill, with a temperature of 103$\frac{3}{5}$° F. A hemorrhagic spot is present on the left knuckle.

March 28. Another chill and a rather copious hemorrhagic eruption appeared on the abdomen, thorax, arms, neck, and lower

part of the back. The spots vary in size from a pinhead to 0.5 x 1.5 cm., red or purplish in color and not raised. No headache or vomiting. He is dull but can be aroused and answers questions. The left arm and neck are rigid and the chin can only be brought within three fingers' breadth of the sternum. Kernig's sign is present, especially in the right side. There is increase of both knee-jerks, slight ankle-clonus, plantar flexion, and a double Oppenheim. The skin reflexes are present, and there is incontinence of urine and feces. Lumbar puncture yielded a small amount of slightly turbid fluid.

March 29. He is soporose and cannot be aroused. Fresh hemorrhages are present in the skin and beneath the conjunctivæ. Leukocytes, 20,900. Urine has continued bloody and albuminous, and shows a trace of bile.

March 30. The left pupil is dilated; slight ptosis and external squint (third nerve paralysis). The pulse is rapid and weak, leukocytes 31,000 and death occurred at 1.15 A.M. on March 31. A blood culture taken on March 29 showed a pure culture of meningococci. The spinal fluid in smears also showed Gram-negative diplococci corresponding in morphologic characters and in pure cultures to the Meningococcus intracellularis meningitides.

Autopsy. Body is that of a well-developed, well-nourished adult white male. Rigor mortis is present. There is lividity of the dependent parts. Pupils 5 mm. and equal. No edema.

Skin. Over the entire body, except the face, neck, hands, and feet, there are scattered innumerable red discrete purpuric, petechial spots, which vary in size from a pinpoint to 0.5 cm. in diameter. Most of these spots are bright red, though a few have a yellowish tinge.

These purpuric spots are separated from each other by 0.5 to 3 cm. of pale normal skin. They are not elevated and do not disappear on pressure. There is no evidence of herpes labialis and no external glandular enlargements.

There are a few bright red hemorrhagic spots in the superficial tissues of the visceral peritoneum covering the cardiac end of the stomach, the small intestine, and the mesentery. They are not nearly so numerous as in the skin.

Pleural Cavity. There are a few cubic centimeters of blood-tinged fluid in each cavity. At the apex of each lung and along the external surfaces of the left upper lobe there are a few old fibrous adhesions.

Pericardial Cavity. There is a slightly increased amount of fluid which is somewhat turbid and tinged with blood. The visceral pericardium covering the right auricle and ventricle is slightly thickened by a smooth grayish tissue.

Heart. Weight, 250 grams. The myocardium is of a moderately deep red color and of fairly firm consistence. The cavities of the heart are not distended. They contain postmortem clot and blood-stained serum. On the auricular surface of the cusps of the mitral valve, close to their line of closure, there is a narrow row of irregular, verrucose, cauliflower-like, grayish-yellow, somewhat pedunculated friable vegetations about 4 mm. in thickness. They are capped with tiny reddish areas. On the ventricular surface of the anterior aortic cusp there is a similar mass of vegetations which measure 3 mm. in diameter. The remaining valves, endocardium, and coronary arteries are normal.

Lungs. Both organs are voluminous and crepitant throughout. On section they are considerably congested. There is no evidence of consolidation.

Spleen. Weight, 390 grams. The surface is wrinkled and the organ as a whole is soft and flabby. On section it is of a dark reddish-brown color, of very friable consistence, and blood drips from it. In the centre of the external surface there is a sharply outlined yellowish area, 0.5 cm. in diameter, which is of firm consistence and is surrounded by a dark red zone.

Gastro-intestinal. The gastric mucosa is considerably congested, otherwise the tract is normal.

Pancreas. Normal.

Liver. Weight, 1900 grams. The external surface is finely granular and of a mottled yellowish-brown color, the yellowish areas being slightly elevated. On section the cut surface is moist and presents the same finely mottled appearance as seen on the surface, and is of fairly firm consistence. The gall-bladder and ducts are normal.

Kidney. Weight, 500 grams. Capsule strips easily, leaving a smooth, dark red moist surface.

Cortex measures 0.5 cm. in width and is of uniform thickness. On the cortex of the left organ there is a slightly elevated, sharply outlined yellowish area 2 cm. x 1 cm. It is of firm consistence, rather dry, and is surrounded by a narrow dark red area. On section the surface is of a deep red color and drips blood. The differentiation between the cortical and pyramidal area is not sharply defined. The Malpighian bodies stand out prominently as bright red points.

Adrenals. Normal. Ureters and testicles normal.

Bladder. The organ is considerably contracted, the walls are thickened, and it contains a small amount of pale turbid fluid. The mucous membrane is pale and shows no hemorrhage.

Organs of the Neck. There is marked congestion of the blood-vessels of the pharynx, larynx, and trachea. The right tonsil is enlarged, measuring 1.5 cm. in diameter, and on its surface there is a flat area 0.75 cm. in diameter, throughout which the superficial tissues are absent. The left tonsil is of normal size and shows no loss of substance.

Brain. External ears, scalp, and calvarium are normal. The great longitudinal sinus contains postmortem clot and blood-stained serum. The dura mater strips easily from the calvarium and underlying pia-arachnoid. The pia-arachnoid along each side of the longitudinal sinus contains considerable serous fluid. There is marked congestion of the vessels of the pia-arachnoid over each hemisphere. This is more marked around each fissure of Rolando where the pia is deeply stained with bright red blood. Over the base of the brain there is a thick layer of yellowish fibrinopurulent exudate. Sinuses at the base of the skull contain postmortem clot and blood-stained serum.

Middle Ears. Normal.

Bone Marrow. Is of a yellowish-red color, apparently normal.

Spinal Cord. There is marked congestion on the vessels of the external surface of the dura mater, especially where the nerve roots emerge. The vessels of the pia mater are considerably congested, but there is no frank exudate.

Anatomical Diagnosis. Acute leptomeningitis (cerebral and spinal); acute endocarditis (mitral and aortic valves); acute hemorrhagic nephritis; acute splenitis with infarction; cirrhosis of the liver; congestion of lungs; chronic pleuritis, adhesive; chronic pericarditis (localized); acute tonsillitis; acute purpuric hemorrhages of skin and peritoneum; bacteriemia.

Bacteriological Report. Two days before death cultures were made from the cerebrospinal fluid which was slightly turbid. From these a pure culture of meningococcus was obtained.

Twenty-four hours before death a blood culture was taken. The skin over the elbow was thoroughly cleansed and 15 c.c. of blood removed from the median Basilic vein. From this blood a series of plain and dextrose agar tubes were inoculated and from them Petri plates poured.

The inoculated media was incubated at 37°. At the end of twelve hours there were a great number of colonies of meningococci on the plates.

At the postmortem cultures were made from the pericardium, heart's blood, central portion of the exudate on the mitral valve, pleural fluid, peritoneal fluid, cortex of the kidney, infarct of the kidney, central portion of the spleen, liver, urine, lung, cerebrospinal fluid, and brain substance. From all these locations, except the peritoneal fluid, the meningococcus was recovered either in pure culture or associated with some other organism. The following technique was employed in taking the cultures from the exudate on the mitral valve: Before the heart was removed, all the afferent and efferent vessels were ligated. After removing the heart, its surface was sterilized by heat, the left ventricle opened with hot sterile instruments, and the cavities of the left side of the heart washed with sterile salt solution until the solution was no longer blood-stained. The surface of the largest mass of exudate on the mitral valve was sterilized with a hot instrument and cultures and smears made from its central portion.

Cultures were made from the central portion of the infarct of the kidney after sterilizing its periphery and cutting into the infarct with sterile instruments.

Pure cultures of the meningococcus were recovered at the autopsy

from the following localities: Central portion of the exudate on the mitral valve, centre of the infarct of the kidney.

Besides the meningococcus the following organisms were isolated from the cultures made at the post mortem: Pleural cavity, B. coli and staphylococcus albus; spleen, B. coli; urine, B. coli and staphylococcus albus; cerebrum, B. coli; liver, B. coli.

The meningococci isolated from the blood, cerebrospinal fluid, and from the post mortem showed the following characters: Gram negative biscuit-shaped diplococci. Some in groups of fours or more, no chains.

Human blood agar: Twenty-four hours. Grayish-white, fairly profuse, moist, round, shiny colonies that have a slight mucoid character. Besides discrete colonies, in places the growth is confluent. Forty-eight hours. Same general character of twenty-four hours' growth. Growth heavier. After forty-eight hours, growth increased but little in amount. The media became brown. Hydrocele agar: Growth of same character as on blood agar. Potato: No visible growth. Smears show very few organisms. Litmus milk: No change. Smears show very few organisms. Plain bouillon: No change after four days. Inulin broth: No change after four days.

Animal inoculation six hours of growth on blood agar washed off with sterile salt and injected intraperitoneally in a guinea-pig and mouse, and through a trephine opening into the meninges of a guinea-pig.

The guinea-pig injected intraperitoneally showed no ill effects. The mouse died in less than twenty-four hours. From the heart's blood a Gram negative biscuit-shaped coccus similar cellularly and in staining reactions to that described above was recovered in pure culture.

The guinea-pig injected meningeally died in twelve hours. No macroscopic exudate in brain. Vessels of pia-arachnoid deeply congested. From the meninges and heart's blood a pure culture of an organism similar in every way to that described above was recovered.

Smears made from the lesions on the heart valves, cerebrospinal fluid, and kidney infarct showed Gram negative biscuit-shaped

diplococci. This organism was present in very great numbers in the valvular exudate. There were also many white blood cells, mostly polynuclear leukocytes and debris. Some of the polynuclear leukocytes contained several organisms in their cytoplasm.

Briefly summarized, this patient was ill for a period of five weeks, of which the last two were spent in the hospital. A diagnosis of malignant endocarditis was made from the presence of fever, cardiac enlargement and a mitral murmur, and the hemorrhagic nephritis was regarded as secondary. During this time there was nothing to suggest involvement of the meninges. The patient was bright and clear mentally, and without cerebral symptoms. Five days before death he became soporose and dull, and after twenty-four hours developed a copious hemorrhagic eruption, rigidity of the neck, and gradually passed into coma.

The meningococci in the spinal fluid indicated the character of the meningeal infection and the blood culture showing the same organism revealed a similar general infection. Unfortunately no blood culture was made until the development of the meningitis, and it was therefore impossible to be positive during life whether the meningococcus was a primary or simply a terminal infection.

The clinical course shows that a general infection with arthritis and endocarditis preceded the meningitis, while the autopsy findings proved definitely the dependence of the endocarditis on a meningococcus infection, the organism being present both in smears and culture, having the characteristic morphological and cultural characters.

The subject of meningococcus infection of the blood and of the endocardium has been so recently and fully treated by Cecil and Soper that there is nothing fresh to be gleaned from the literature of the subject. These writers report a case of meningococcus endocarditis and septicemia without involvement of the meninges, including very full bacteriological details. Meningococci were found in blood cultures during life. At autopsies smears from the cardiac valves showed similar organisms, but a culture revealed only a single colony of the colon bacilli. Cultures from other tissues also showed only B. coli and a few streptococci. The writers

believe that the B. coli and streptococci were terminal or post-mortem invaders.

Four other cases of endocarditis believed to be due to the meningococci were collected by Cecil and Soper, three of which occurred in typical cases of meningitis, but lacked bacteriologic examination of the endocardial vegetations. The fourth case, reported by Warfield and Walker presents conclusive bacteriological evidence of a malignant meningococcus endocarditis. There was no meningitis.

In addition to these cases of endocarditis Cecil and Soper collected five cases of septicemia due to meningococci. In one of these (Salomon's) meningitis developed after a two month's illness in the other four the meninges remained free.

Conclusions: From the above cases it may be concluded that meningococci may primarily infect the blood and lead to acute endocarditis, and further, that the meninges may altogether escape or become involved only at a late period of the disease.

IMMUNIZATION BY MEANS OF CULTURES OF TRYPANOSOMA LEWISI[1]

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In a previous paper[2] it was shown that cultures of *Tr. Lewisi* when plasmolyzed in collodium sacs, against distilled water, underwent changes resulting apparently in complete solution or rather disintegration of the organisms. Three or more injections, on alternate days, of such plasmolyzed cultures protected young rats against a minimal infective dose of virulent blood. Immunity could therefore be produced by the injection of disintegrated cultural trypanosomes.

At the time it was also pointed out that cultures of *Tr. Lewisi* and *Tr. Brucei*, even after they had passed through a hundred generations or subcultures, in the course of two years, do not become attenuated by such prolonged consecutive passage but readily infect. This statement is only partially true, since the organisms on prolonged cultivation actually do suffer some loss of virulence or capacity to infect. A culture of *Tr. Brucei* in the one-hundredth generation will infect rats but the period of incubation is somewhat lengthened, and while death may occur within two or three weeks it may not result until several months have elapsed from the time of inoculation; the longest survival is one which is at present in its two hundred and fifty-third day. Obviously, the

[1] This research has been aided by a grant from the Rockefeller Institute.

[2] Novy, Immunity against Trypanosomes, Proc. Soc. Exp. Biol. and Med., 1907, iv, 42.

conditions which obtain in cultivation, notably the composition and reaction of the medium, the temperature and duration or age of culture, are not without appreciable effect on these organisms.

From the beginning, when the cultivation of *Tr. Lewisi* and *Tr. Brucei* was first effected, we have looked forward to the production of attenuated strains which could be utilized in preventive inoculations. It seemed reasonable to believe that the cultures of pathogenic protozoa, like those of bacteria, would be found available to some extent in the production of immunity. The fact that spontaneous recovery may occur in protozoal diseases, as is the case with relatively insusceptible species, indicates the establishment of an acquired immunity, and hence the inherent capacity possessed by such animal to protect itself against the given parasite. The trypanosomal infection of the common rat is a most excellent illustration of this fact since it only exceptionally proves fatal. In the course of some weeks, or months, the rat gets rid of the trypanosome and becomes immune to a subsequent inoculation. It is evident, therefore, that the cultures of this parasite are particularly suitable for work bearing upon trypanosomal attenuation and immunity. With this organism it has been possible to demonstrate two important facts: (1) that attenuation can be secured, and (2) that such living, attenuated cultures confer a solid and permanent immunity.

The culture of *Tr. Lewisi* which we have used was isolated from a rat September 5, 1905, since which time it has been maintained on ordinary blood-agar medium at 25°. It is at present in the three hundred and thirteenth generation. At first the culture was readily infective, the growth from a single tube being sufficient to produce typical infection in the rat. This infective property persisted for a considerable period and was frequently utilized to supply infected rats for the laboratory. After a long interval, in March, 1909, this procedure to secure a rat infection was again resorted to, the culture then being in the one hundred and fifty-eighth generation. Contrary to expectation no infection resulted. During the next few weeks no less than seventeen were tested by intraperitoneal injections, each receiving from two to four cultures. In every case, as before, the result was negative, although daily

examinations were made for an entire month. These tests clearly demonstrated that this stock culture of *Tr. Lewisi* had completely lost its capacity to develop within the rat. In other words, it had become fully attenuated.

The many inoculations made with this culture during the last three years have invariably failed to produce infection. The result is the same whether the contents of a single tube or of fifty tubes is injected into the rat. Such cultures, grown at 25° for seven to ten days, were extremely rich in flagellates, which at times formed a thick slimy covering on the blood-agar medium. Hence, the quantity of flagellates injected was at times enormous, and yet notwithstanding this fact no infection could be produced. The microscopic appearance of the cultures was nowise different from that of the early generations, which gave positive results, but the parasitic property of the organism was definitely lost.

All attempts to restore the infectious character to the culture have been fruitless. Even when the culture was placed in collodium sacs, in the peritoneal cavity of rats, it failed to multiply. Possibly further efforts in this direction may be successful.

While it is true, as has been emphasized above, that the cultures are no longer infective, it is an interesting fact that the majority of the inoculated rats do show in their blood, within the next day or two, a small number of fairly typical blood trypanosomes. These, however, do not increase in numbers and usually disappear within forty-eight hours after the injection. After that they are not to be found even though most careful examinations are made for a month or more. With the hope of restoring the virulence, the blood of rats showing these early trypanosomes was drawn from the heart and injected[1] into clean young rats and was also planted at the same time on blood agar. Much to our surprise, it was found that such blood failed to infect the rats and also failed to give cultures in the tubes.

The failure to secure a growth on the blood-agar medium was particularly surprising, since, as is well known, this cultural method is capable of revealing trypanosomes even when prolonged microscopic examinations are negative. In all, about twelve rats which

[1] All injections, unless otherwise indicated, were given intraperitoneally.

showed these transitory trypanosomes were cultured without obtaining the slightest indication of a growth. Similarly, the inoculation of nine rats with such blood, the doses varying from $\frac{1}{4}$ to 3 c.c., failed to infect. Here, as above, the negative result could not be ascribed to the small number of trypanosomes, for it can be readily shown that the normal trypanosomal blood will infect when diluted to such an extent that the parasites can scarcely be detected under the microscope. Likewise, the susceptibility of our rats could not be called into question. In all of our work special care was taken to use only young rats, weighing from 60 to 90 grams, which had been repeatedly examined for two or more weeks and thus found to be free from natural infection. When used as controls, the injection of 1 c.c. of a 1 to 10,000 dilution of blood containing *Tr. Lewisi* invariably gave a rich infection.

It is evident, therefore, that the trypanosomes which appear transitorily in the blood of rats after the injection of a culture are incapable of further multiplication or reproduction. They are sterile or abortive forms, and without doubt their further study will prove of interest. It would seem as if some of the cultural trypanosomes still possessed a tendency to develop into the blood form, but the resulting individual through lack of inherent vigor or failure of fertilization(?) is unable to develop any farther and soon disappears.

It is probable that these abortive forms are present in the blood of all rats inoculated with the cultures. They are, however, easily overlooked and for that reason they have been found in only 75 per cent. of the rats examined. They have been observed in the blood on one occasion five hours after the injection; at other times within twelve hours, but more often between twenty-four and forty-eight hours. Only exceptionally have they been seen as late as seventy-two hours, and once they were observed to be present for four days. As already stated the abortive forms are to be found in small numbers only. At times, after a prolonged search, but a single one can be found; more often, one can be found for every five or ten fields (No. 7 objective); and, rarely, one for every two fields examined. The number of abortive forms is independent of the dose injected, for in rats which received fifty cultures they were no

more numerous than when a single culture was given. Likewise, the age of the culture seems to have no influence upon the number of these forms.

IMMUNITY

As already stated our previous studies have shown that cultures of *Tr. Lewisi* when plasmolyzed[1] were capable of producing immunity in rats. It was therefore to be expected that the living attenuated cultures would behave in a similar way and confer protection against the blood trypanosome. The experimental work in this direction demonstrated that such was the case and that an active immunity was developed in animals which had received single or multiple injections of the living cultures.

In order to obtain absolutely conclusive results it was necessary to employ young rats, preferably those raised in the laboratory, which repeated examinations for at least two weeks before use had shown to be free from the natural infection. In the beginning, when rats which had been purchased on the market were used, it not infrequently happened that the control animals in an experiment would fail to become infected, thus invalidating the immunity test. This difficulty was entirely overcome by employing only carefully tested young rats.

Another point of importance, not infrequently lost sight of in immunity tests, is the use of a very small but surely infective dose of the virulent organism, for the reason that a given degree of immunity may be effective against a minimal infecting dose, but not against a hundred or thousand doses. A very large dose of virus may readily break down a slight immunity and thus lead to the erroneous conclusion that no protection exists. With this consideration in mind, we have as a rule employed the test virus in a dilution (in 0.85 per cent. salt solution) of 1 to 10,000. One cubic centimeter of this suspension has never failed to produce a rich infection in clean young rats. In some instances, as shown in the tables, suspensions of 1 to 200 or 1 to 2000 were used.

[1] This method of preparing a vaccine, though not generally applicable, has been utilized in this laboratory by Dr. J. G. Cumming, in charge of the University Pasteur Institute, in the preparation of a safe antirabic vaccine. His experiments have shown that the dialyzed virus protects animals even more efficiently than does the desiccated virus prepared in the ordinary way.

TABLE I.—Immunity Tests Made after a Single Injection of

Two cultures.					Six cultures.				
Rat No.	Interval between injections.	Test dose of Tr. Lewisi blood.	Result.	Remarks.	Rat No.	Interval between injections.	Test dose of Tr. Lewisi blood.	Result.	Remarks.
1	14 days	0.005 c.c.	⊙	One trypanosome on third day.	18	14 days	0.005 c.c.	0	
2	14 days	0.005 c.c.	0		19	14 days	0.005 c.c.	0	
3	2 days	0.0005 c.c.	+	Rich infection.	20	2 days	0.005 c.c.	+	Rich infection.
4	18 days	0.0005 c.c.	0		21	2 days	0.0005 c.c.	+	Rich infection.
5	4 days	0.0001 c.c.	0		22	18 days	0.0005 c.c.	0	
6	9 days	0.0001 c.c.	0		23	4 days	0.0001 c.c.	⊙	Very mild infection. $\frac{1}{10}$ per field for 3 days.
7	13 days	0.0001 c.c.	0		24	9 days	0.0001 c.c.	0	
8	16 days	0.0001 c.c.	⊙	Very mild infection, 1 per field for 7 days.	25	13 days	0.0001 c.c.	0	
					26	16 days	0.0001 c.c.	0	
9	3 days	0.0001 c.c.	+	Rich infection.	27	3 days	0.0001 c.c.	+	Rich infection.
10	8 days	0.0001 c.c.	+	Rich infection.	28	8 days	0.0001 c.c.	⊙	Very mild infection. 1 per field for 6 days.
11	12 days	0.0001 c.c.	0						
12	16 days	0.0001 c.c.	0						
13	10 days	0.0001 c.c.	0		29	17 days	0.0001 c.c.	0	
14	10 days	0.0001 c.c.	⊙	Very mild infection, 1 per field for 9 days.	30	17 days	0.0001 c.c.	0	
15	10 days	0.0001 c.c.	0		31	17 days	0.0001 c.c.	0	
16	10 days	0.0001 c.c.	0		32	17 days	0.0001 c.c.	0	
17	10 days	0.0001 c.c.	0		33	17 days	0.0001 c.c.	⊙	Very mild infection. $\frac{1}{5}$ per field for 4 days.

In the tests tabulated above, controls were inoculated every time after the experimental animals and developed a rich and lasting infection.
0 indicates no infection, *i. e.*, immunity is present.
+ indicates a rich infection, the same as that in the controls.
⊙ indicates a mild or abortive infection, characterized by the presence of very few trypanosomes per field in fresh blood preparation.

On examination of Table I several interesting facts will be noted. When the interval between the injection of the vaccine and the test dose is but two or three days (Rats Nos. 3, 20, 21, 9, 27) a rich infection results showing that little or no immunity exists at that time. Possibly a smaller dose of the test virus might have shown some immunity at this early date because this is certainly in evidence on the fourth day (Nos. 5 and 23). On the other hand, but one of the two rats inoculated on the eighth day (No. 28 which received six cultures) developed sufficient resistance to abort the infection.

Very mild or abortive infections may occur, as will be seen, in rats inoculated even on the tenth (No. 14), fourteenth (No. 1), and seventeenth (No. 33) day, but in these the parasites were as a rule very scanty and persisted for but a few days. These infections correspond to those which can be produced by injecting a large dose of trypanosomal blood into rats which have recovered from a natural infection. The breaking down of the immunity in such cases is usually indicated by a mild infection of but a few days' duration.

Altogether it will be evident that immunity is produced by the injection of living cultures of *Tr. Lewisi* and that this immunity is most pronounced after the lapse of about ten days. In the experiments discussed, the smallest dose of vaccine was represented by the growth present in two culture tubes.[1] The minimum dose of the living culture, sufficient to immunize, is probably a very small fraction of that mentioned. Thus in one experiment four rats were inoculated with the growth corresponding to $\frac{1}{4}$, $\frac{1}{2}$, 1, and 2 culture tubes respectively. After an interval of twelve days these rats and two controls were inoculated with 0.0001 c.c. of trypanosomal blood; the treated rats showed no infection, whereas the controls became heavily infected.

Subcutaneous Injection of Cultures. As might be expected a notable difference in immunity production is obtained according to whether the vaccine is introduced intraperitoneally or subcutaneously. When

[1] The tubes used for cultures were small, being but 12 by 150 mm. After inoculation the tubes were placed in a hot room at 25° for from seven to twelve days. The growth was then taken up in 0.85 per cent. salt solution and at once injected.

It may be stated in this connection that the injection of an extract from uninoculated tubes has no immunizing action.

introduced by the latter route a much larger dose of the culture must be given in order to obtain protection. Only one experiment with single injections, given subcutaneously, was made and is worthy of note. As shown in Table II the rats which received two cultures became infected as heavily as did the controls; whereas those which received six cultures at the same time showed a mild abortive infection which persisted for one and three days respectively. Evidently a single injection given subcutaneously is much less effective than when given intraperitoneally, for while a fraction of a culture is sufficient when administered by the latter route, a much larger dose is necessary when injected under the skin.

When several injections are given subcutaneously the resulting immunity is much more marked, since the absorption of the antigen is necessarily greater. One experiment of this kind is given in Table II and shows perfect protection.

TABLE II.—Immunity Tests after Subcutaneous Injection of Living Cultures

Rat No.	Received.	Interval before test dose.	Test dose of Tr. Lewisi blood.	Result.	Remarks.
1	2 cultures	18 days	0.0001 c.c.	+	Rich infection.
2	2 cultures	18 days	0.0001 c.c.	+	Rich infection.
3	6 cultures	18 days	0.0001 c.c.	⊙	Mild infection for 3 days.
4	6 cultures	18 days	0.0001 c.c.	⊙	Mild infection for 1 day. Two controls gave a rich infection.
5	5 injections in 5 days, each of 2 cultures	17 days	0.0001 c.c.	0	Perfect immunity.
6	5 injections in 5 days, each of 2 cultures	17 days	0.0001 c.c.	0	Perfect immunity.
7	5 injections in 5 days, each of 2 cultures	17 days	0.0001 c.c.	0	Perfect immunity. Four controls gave a rich infection.

MULTIPLE INJECTIONS

In Table II, Nos. 5, 6, and 7 show that multiple injections of the culture given subcutaneously impart a marked degree of immunity. A number of similar tests were made, the injections being intraperitoneal, in order to obtain hyperimmunity and to test the resistance of such rats to relatively large doses of trypanosomal

blood. The rats thus immunized, while fully protected against a minimal dose of virus, on the injection of a fairly large dose, such as 0.25 c.c., may show a mild abortive infection which disappears in from two to three days. An exactly similar "breakdown" of immunity frequently occurs when a large dose of infective blood is injected into rats which have spontaneously recovered from an infection with *Tr. Lewisi*. These abortive infections depend largely upon the dose and to some extent upon the rat itself.

The result of these tests is given in Table III. By way of explanation it should be stated that Nos. 1 to 4 received in the course of twelve days three injections, each of six cultures; Nos. 5 to 7, in fifty-eight days, received three injections each of two cultures, while Nos. 8 to 10 in the same time were given also three doses, each of four cultures, and Nos. 11 to 13 received similar injections each six cultures. Nos. 14 to 21 were given in the course of sixty-seven days six injections, the first four receiving each time two and the last four six cultures.

TABLE III.—Immunity after Multiple Injections

Rat No.	Received.	Interval before test dose.	Test dose of Tr. Lewisi blood.	Result.	Remarks.
1	3 x 6 C 12 days	13 days	0.25 c.c.	⊙	Trypanosomes present for 2 days.
2	3 x 6 C 12 days	13 days	0.25 c.c.	⊙	Trypanosomes present for 3 days.
3	3 x 6 C 12 days	13 days	0.25 c.c.	0	Full protection.
4	3 x 6 C 12 days	13 days	0.25 c.c.	⊙	Trypanosomes present for 2 days. Four controls gave rich infection.
5	3 x 2 C 58 days	5 days	0 1 c.c.	0	
6	3 x 2 C 58 days	5 days	0.1 c.c.	0	
7	3 x 2 C 58 days	5 days	0.1 c.c.	⊙	Trypanosomes present for 4 days.
8	3 x 4 C 58 days	5 days	0.1 c.c.	0	
9	3 x 4 C 58 days	5 days	0.1 c.c.	0	
10	3 x 4 C 58 days	5 days	0.1 c.c.	0	Two controls for this set (Nos. 5 to 13) gave rich infection.
11	3 x 6 C 58 days	5 days	0.1 c.c.	0	
12	3 x 6 C 58 days	5 days	0.1 c.c.	0	
13	3 x 6 C 58 days	5 days	0.1 c.c.	0	
14	6 x 2 C 67 days	7 days	0.005 c.c.	0	This set of 8 were injected two weeks later with 0.25 c.c. of virulent blood. All resisted perfectly this second injection. Four controls for this set gave rich infection.
15	6 x 2 C 67 days	7 days	0.005 c.c.	0	
16	6 x 2 C 67 days	7 days	0.005 c.c.	0	
17	6 x 2 C 67 days	7 days	0.005 c.c.	0	
18	6 x 6 C 67 days	7 days	0.005 c.c.	0	
19	6 x 6 C 67 days	7 days	0.005 c.c.	0	
20	6 x 6 C 67 days	7 days	0.005 c.c.	0	
21	6 x 6 C 67 days	7 days	0.005 c.c.	0	

DURATION OF IMMUNITY

Since a single injection of the living culture protects against a surely infective dose of *Tr. Lewisi* it was of interest to ascertain the duration of such immunity. This active immunity becomes manifest in about ten days and once developed it probably persists until the death of the animal. Up to the present time we have not tested out the immunity for a longer period than five months, but there can be little doubt that it will be found to last for a considerably longer period.

In Table IV, which may be looked upon as a continuation of Table I, are brought together the several tests in which the interval between the injection exceeds eighteen days. The several groups were tested at different times with the usual dose of 0.0001 c.c. of trypanosomal blood. In every case controls were inoculated at the same time and invariably gave a rich infection.

TABLE IV.—Duration of Immunity Following the Single Injection of Living Cultures

Rat No.	Received.	Interval before test dose.	Test dose of Tr. Lewisi blood.	Result.	Remarks.
1	2 cultures	35 days	0.0001 c.c.	0	
2	2 cultures	35 days	0.0001 c.c.	0	
3	6 cultures	42 days	0.0001 c.c.	0	
4	6 cultures	42 days	0.0001 c.c.	0	
5	6 cultures	74 days	0.0001 c.c.	0	
6	6 cultures	74 days	0.0001 c.c.	0	
7	2 cultures	78 days	0.0001 c.c.	0	
8	2 cultures	78 days	0.0001 c.c.	⊙	A single trypanosome was found on each of two days.
9	2 cultures	84 days	0.0001 c.c.	0	
10	2 cultures	84 days	0.0001 c.c.	0	
11	2 cultures	112 days	0.0001 c.c.	0	
12	6 cultures	119 days	0.0001 c.c.	0	
13	2 cultures	150 days	0.0001 c.c.	0	
14	6 cultures	159 days	0.0001 c.c.	0	

IMMUNIZATION AGAINST NATURAL INFECTION

The marked protection following the introduction of living cultures suggested the possibility that vaccinated rats would be equally protected against natural infection by the flea or louse.

The number of parasites present in the test dose of blood employed in the previous experiments must be considerably larger than can be introduced through the agency of a biting insect. If, therefore, no other factor is involved it should be possible to protect the rats against the natural infection by means of insects.

The white rat which we have used exclusively has never been found in this laboratory to harbor fleas and consequently we have been unable to undertake experiments with this insect. The rats, however, are often heavily infested with lice, and since, unquestionably, these as well as fleas are agents of transmission we endeavored to protect the rats against this source of infection.

In our first experiment we tried to secure infection by the direct transfer of lice from infected rats to a set consisting of four clean and four vaccinated rats, each of the latter having previously been given an injection of six cultures. Although considerably over a hundred lice were transferred to each rat no infection followed. Later on, therefore, these rats were confined in a small space with infected rats which were heavily infested with lice, but the result was no better. At the end of five months, although blood examinations were made twice weekly for over four months, no trypanosomes could be detected in the exposed rats. The failure of the controls to become infected was not due to an unrecognized infection, since one of these inoculated on the one hundred and thirty-third day with 0.0001 c.c. of virulent blood gave a typical infection.

For the second experiment ten rats were injected each with six cultures. Five of these (see Table I, Nos. 29 to 33) were tested seventeen days later and found to be immune. The remaining five, together with five clean rats for control and five rats containing *Tr. Lewisi* and heavily infested with lice, were placed in a small cage, where they remained for several months. The rats were examined at least once a week for two months, but no spread of the infection occurred.

A third experiment was more successful. As above, ten rats were first injected each with two cultures, and after ten days five of these were tested and found to be immune (see Table I, Nos. 13 to 17). The remainder, together with five clean and eight lousy infected rats, were confined in a small cage. Later on five

additional infected and lousy rats were added. Of the vaccinated rats four died on the twenty-fourth, twenty-ninth, fifty-second, and one hundred and thirtieth day respectively without at any time showing trypanosomes in their blood. Of the five clean controls, two died on the sixty-first and one hundred and sixth day without becoming infected. The remaining three became infected on the twenty-eighth, sixty-ninth, and eighty-first day. The fact that three out of five non-immunes and none of the vaccinated animals became infected would indicate that the living vaccine does protect against infection by the louse. Further tests, however, especially with directly transferred lice, will be necessary to fully establish this point. It seems from the work done thus far that the lice from young rats, which have been inoculated with *Tr. Lewisi* but a few days before, are more likely to convey the infection than those from rats having an old chronic infection.

CURATIVE ACTION OF CULTURES

The readiness with which the living culture immunizes against infection opens the possibility of using such material to abort or, in other words, cure an infection already under way. The extremely rapid and heavy infection in the case of *Tr. Lewisi* makes this at the outset a very unpromising attempt; for when a relatively small dose of trypanosomal blood, as shown in Table III, may serve to break down an existing immunity, it is very probable that the enormous number of parasites in the infected animal will exert a corresponding action and hence completely overwhelm any resistance which might be produced by the vaccine. Possibly repeated inoculation of large quantities of vaccine might eventually give rise to an amount of antibodies sufficient to check the parasites present.

Before, however, undertaking to put an end to a well-developed infection it was desirable to ascertain whether it was possible to check an infection at the very beginning; in other words, to prevent it by the simultaneous injection of virus and vaccine. In one experiment of this kind, three young rats received an intraperitoneal injection of 0.0001 c.c. of trypanosomal blood. Two of these were reserved for controls while the third was given, likewise

intraperitoneally, within an hour, a suspension of the growth from fifty cultures. A fourth rat also received fifty cultures and served as control. It showed a few abortive trypanosomes on the first two days, but otherwise no sign of infection. Trypanosomes did not appear in the controls until the third day, and then in very small numbers, about one in every ten fields of the fresh blood. In the treated rat, on the contrary, they appeared on the first day, two per field on the second, and four per field on the third day. Some blood drawn from the tail of this rat on the second day and injected into another produced a typical infection, thus demonstrating that the trypanosomes present were not of the abortive type. The appearance of the trypanosomes in the treated rat so much earlier than in the untreated controls is an interesting fact which was corroborated in the second experiment.

Although the trypanosomes in the untreated controls appeared later than in the treated rat, yet once present, they multiplied more rapidly and in three days were several times more numerous than in the latter. On the seventh day they approximated, roughly speaking, about two hundred per field, and this rich infection was maintained during the following three weeks. In the treated rat the maximum number was about one hundred per field on the eighth to the eleventh day; the parasites then decreased and disappeared on the thirtieth day, at which time both controls still showed a maximum infection. This experiment indicated that the injection of a sufficiently large dose of vaccine, shortly after the infective dose, modifies somewhat the course of the infection. The result, however, was not as sharp and conclusive as might be desired.

Consequently, a second experiment was made. Two rats were given an infective dose of 0.0001 c.c., as before. One of these was given one hundred cultures, in three injections, during the next three hours. In this treated rat, as in the one mentioned above, trypanosomes were found on the first and second days, at which time none could be found in the control. Stained preparations made at this time showed that the trypanosomes were nearly all of the large "female" type, many of which were undergoing active division, as indicated by the presence of double nuclei,

blepharoplasts, and even of double flagella. Minute flagellates, such as are formed by the breaking up of the eight-celled rosette, were also noted. Of special interest is the fact that though the trypanosomes appeared earlier than in the control they did not continue to increase as they did in the latter.

In the treated rat the trypanosomes, at first, appeared to be stimulated to very rapid multiplication, but this was soon checked, and then actually the number was greatly decreased so that on the sixth and seventh days on an average not more than one could be found in every two fields of a fresh blood preparation. After this there was a gradual rise, and although the rat was examined for twenty-six days the number never exceeded about seventy-five per field. The course of the infection in this treated rat, even more so than that in the first experiment, is indicative of a marked inhibitory influence and points to the possibility of aborting an infection by repeated large doses of the vaccine.

The course of the infection in the rats of this last experiment can best be seen from the following summary. The figures there given express roughly the number of trypanosomes present, per field of the No. 7 objective, of a fresh blood preparation. Thus, $\frac{1}{10}$ is to read as one trypanosome in ten fields; three as that many per field, etc.

Inoculated	Examined.											
February 26	27	28	29	March 1	2	3	4	5	6	7	8	9
Treated rat . .	$\frac{1}{10}$	3	10	10	5	$\frac{1}{2}$	$\frac{1}{2}$	5	10	10	25	50
Control rat . .	—	—	$\frac{1}{20}$	15	75	100	150	200	200	200	250	Dead.

PASSIVE IMMUNITY

Since the animals treated with one or more injections of living cultures develop a very marked immunity it was to be expected that their blood would carry antibodies and consequently no special effort has as yet been made to otherwise demonstrate their presence. Three tests, however, of a preliminary character were made with the blood of rats which had received several spaced injections. These tests, like the curative experiments given above, were intended to ascertain the effect of simultaneous injections of virus

and hyperimmune blood. The results, it will be seen, are by no means satisfactory.

Exp. No. 1.—The immunized rat received seven injections, each of four cultures. After an interval of one hundred and fifty-three days, 1 c.c. of blood was drawn from its heart and injected into a clean young rat. This was followed at once by an injection of 0.0001 c.c. of trypanosomal blood. A like dose of the virus was given at the same time to two controls and to the hyperimmune rat. The controls developed the typical rich infection, whereas the latter, as expected, resisted perfectly, although five months had passed since the last protective inoculation. The rat which received the dose of immune blood became infected the same as the controls. Apparently the blood was without protective action.

Exp. No. 2.—The immunized rat received four injections, each of six cultures. Seventeen days after the last inoculation it was bled and two rats were injected with its blood, receiving 2.0 and 0.5 c.c. respectively. Within a minute, these two rats and two controls were each given 0.0001 c.c. of trypanosomal blood. The rat which received 2 c.c. of the immune blood had a period of incubation of five days; the other three rats showed parasites on the third day. Otherwise, there was no difference, the severity of the infection in the treated rats being the same as in the controls. Here again, the blood seemed to be without any protective action.

Exp. No. 3.—The immune rat in this test had been given a total of thirty-four cultures in six injections. It was bled after an interval of thirty-one days and two rats were given respectively 3.0 and 1.0 c.c. of its blood. This injection was followed within four minutes by the usual dose of trypanosomal blood (0.0001 c.c.). The same dose of virus was given to two controls and to two young rats born of a mother which had received an injection of two cultures. The latter and the controls gave like rich infections. The treated rats, while they possibly showed fewer trypanosomes on the first two days of the infection, eventually gave as rich infections as the controls.

It is evident that in these three tests passive immunity was not conferred. Had the immune blood been injected one or two days previous to the infective dose, the result might have been different.

To protect against the virus, when given simultaneously, a much larger dose of blood is needed, or else the blood must come from animals which are more highly immunized.

EFFECT OF BERKEFELD FILTRATES OF PLASMOLYZED CULTURES

Since living as well as dead plasmolyzed cultures immunize against infection with *Tr. Lewisi* it may be pertinent to inquire whether this immunity is due entirely to the solid intracellular constituents or whether soluble products are in any way concerned. In order to obtain some light on this point, a large number of cultures (one hundred and twenty) were prepared. The growth was taken up in 0.85 per cent. salt solution and transferred to collodium sacs, immersed in running distilled water, and subjected to plasmolysis for eighteen hours. At the end of that time the flagellates had disintegrated or rather shrunk to small rounded forms. The contents of the sacs were then centrifugated at 8000 revolutions, to remove the cell detritus, and the clear liquid was passed through a small Berkefeld filter. The filtration, aided by an aspirator, was rapid and required but a few minutes.

The clear filtrate was injected into six pairs of rats; the rats of each pair receiving the equivalent of two, four, six, twelve, twelve, and twenty-four cultures respectively. Twelve days later each of these as well as four controls received 0.0001 c.c. of trypanosomal blood. One of the treated rats which received the equivalent of four cultures gave a mild infection which cleared up on the ninth day. All of the other treated rats developed as rich infections as did the controls and consequently the single exception referred to is of no significance. The only conclusion which can, therefore, be drawn from this test is that the Berkefeld filtrates of plasmolyzed cultures have no immunizing properties. It may be added, parenthetically, that the same fact has been noted by Dr. Cumming in connection with his studies (unpublished) on rabic virus. While plasmolyzed suspensions of this virus confer a marked immunity, the filtrates of such suspensions are inert. In other words, it would seem that the insoluble constituents of the cultures, as well as of the rabic virus, are essential to the production of the immunity.

SUMMARY

Tr. Lewisi after cultivation for several years on rabbit blood-agar medium becomes non-infective.

Trypanosomes may appear in very small numbers in the blood of rats inoculated with such cultures, but they are incapable of multiplication *in vitro* or *in vivo*.

Rats which have received one or more injections of the living culture acquire a solid immunity which becomes apparent in about ten days.

The immunity produced by the living culture is lasting and probably persists through life.

The immunity induced by the living vaccine is probably efficacious against the natural transmission through the flea and louse.

The immunity is not due to soluble products, since plasmolyzed and filtered cultures are inert.

This successful immunization against *Tr. Lewisi* by means of a living vaccine renders it probable that like results may be obtained with the more strictly pathogenic trypanosomes. It may be added that encouraging results have already been obtained with *Tr. Brucei*.

POISONING BY NITRIC OXIDE FUMES

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This case of fatal poisoning by nitrogen tetroxide fumes is reported for its medico-legal interest and also because of the rarity of the condition and a general lack of recognition of the pathologic changes in the lungs of persons dying from the action of this very dangerous gas.

When nitric acid acts upon certain metals, such as copper, silver, or cadmium, a gas is given off with the composition of NO or nitrogen dioxide. When this gas comes in contact with the air it absorbs oxygen, with the production of nitrogen tetroxide or N_2O_4. If either of these compounds of nitrogen and oxygen comes in contact with moisture, nitrogen dioxide forms nitric acid, while nitrogen tetroxide is slowly decomposed into nitric and nitrous acid. These are the decompositions which occur when brown fumes are given off by the action of nitric acid on the substances mentioned above.

When strong nitric acid acts upon organic bodies it produces nitrogen trioxide. This immediately decomposes, however, into a mixture of nitrogen trioxide and nitrogen tetroxide. The nitrogen trioxide is continuously converted into nitrogen tetroxide by the action of the atmospheric air. Inhalation of these gaseous compounds occasionally occurs in laboratories or factories in which considerable quantities of these fumes are formed either during the course of some reaction or when a carboy of nitric acid is spilled.

The inhalation of nitrogen tetroxide vapor, if not too concentrated, causes at first no symptoms, with the exception of a slight tendency to cough and an acid taste in the mouth. It has occasionally been observed that workmen have remained for some hours

in a room in which nitric acid has been spilled without showing any evidences of injury, or that if on feeling uncomfortable they went into the open air the symptoms have disappeared rapidly, only to recur in full force six to eight hours later. If the vapors are concentrated, the patient may suffer immediately from severe dyspnea, a feeling of pressure on the chest, coughing, faintness, and cyanosis. Dyspnea and slight cyanosis are the frequent symptoms; the patient often on reaching the air also vomits any food that may be in the stomach and then feels perfectly well for a period of six or eight hours. At the end of this time, often without any inciting cause, sometimes while the patient is quietly seated or asleep in bed, there is a sudden attack of extreme dyspnea, with a sense of oppression in the chest, or a feeling of anxiety, so that the cases resemble acute attacks of asthma. Usually there is a good deal of thirst and a sense of suffocation. A cold sweat breaks out on the features, the eyes protrude, and the patient talks with difficulty. From time to time paroxysms of coughing occur, lasting from ten to fifteen minutes and terminating in vomiting. Cyanosis is regularly present. The mind is perfectly clear. The patient usually dies within forty-eight hours, though in some cases death has not occurred for five to eight days or more rarely two to three weeks.

The blood is dark in color, but generally shows only oxyhemoglobin.[1] The urine may show albumin and blood pigment (in one case hematin), but not constantly. Death occurs in consequence of edema of the lungs, and is usually preceded by the expectoration of a good deal of foamy yellowish fluid and evidence of cardiac failure. In some cases severe diarrhea and collapse are observed, but this is not a frequent form of termination.

In patients who have inhaled small amounts of gas and have improved after the first attack of edema of the lungs, the disease may continue for a number of days with the clinical symptoms of acute bronchitis and evidences in the chest of lobular or lobar pneumonia. Usually there is extreme dyspnea. The sputum is tenacious, yellowish or brown. Vomiting may be so extreme as to

[1] Czaplewski was able to demonstrate methemoglobin in only one out of twelve cases of severe poisoning, and this was not a fatal case.

mask the pulmonary symptoms, though as a rule this is uncommon. Such cases may recover, but often show an increased liability to bronchitis or pneumonia for months afterward.

At autopsy the larynx, trachea, and bronchi are congested and of a reddish or brownish color. If the patient dies shortly after exposure the lung is edematous; in those living for several days, it is emphysematous with, in addition, a moderate amount of pneumonic exudate. The vessels of the lungs often contain thrombi. From the cut surface exudes a reddish or brownish fluid. In the other organs ecchymoses are occasionally found. Focal necroses may occur in the liver. The meninges are often congested, and there are occasionally punctate hemorrhages throughout the substance of the brain. The kidneys have in a few cases shown acute degeneration or acute nephritis; generally, however, they are not much altered.

The number of published cases of death following the inhalation of vapors of nitrogen tetroxide is not very large; but owing to the greatly increased use of nitric acid in the arts, cases of such poisoning are likely to be more frequent in the future, and they may also assume a medico-legal importance in connection with accident insurance and employers' liability acts. On this account the following fatal case is reported together with the results of animal experiments and a survey of the cases already published.

The patient, D., in this instance, accidentally inhaled the fumes arising from a large vessel containing considerable quantities of nitric acid and a cadmium-silver alloy. The room in which the experiment was conducted was small, and the patient experienced some discomfort and a sensation of choking, and went into the open air. After a few minutes he vomited and then felt much better. There were no further symptoms until some six or eight hours later, when he was seized with intense dyspnea, and collapsed. Twenty-four hours later he entered the hospital, remaining there until his death seven days after the exposure. On admission he complained chiefly of weakness, pain in the throat and chest, and intense dyspnea.

Examination showed a well-nourished man with slightly dilated heart, rapid feeble action, soft pulse. He was suffering at the time

of the examination from very severe dyspnea, with extremely rapid, shallow respiration, and marked cyanosis. Prostration was very extreme, but the patient's mind was clear. The pupils were equal and reacted. The lips and tongue were intensely cyanosed; the throat was congested. The lungs showed marked dulness at both bases posteriorly; bronchovesicular breathing, with slightly bronchial voice and scattered rales, most marked over right base. The extremities were cold and blue. The temperature ranged from 100° to 102° F.; the pulse from about 100 to 140; respiration from 44 to 60, during the patient's stay in the hospital. He was given oxygen inhalations, and blood was drawn for examination. It was very dark in color but when examined spectroscopically showed oxyhemoglobin only and no evidence of carbon monoxide[1] or methemoglobin. Under the stimulation of the oxygen inhalations the patient got along fairly satisfactorily for several days. Examination of the urine showed: Specific gravity, 1.026; albumin, 2 per cent. by volume; a few leukocytes, mucus, and red cells; no casts. Repeated examinations gave the same findings, except that three days before death the urine contained a trace of albumin only and a few hyaline casts. The day before the patient died there was 5 per cent. of albumin by volume, with a few hyaline and granular casts.

During the past few days the patient's respiration was very difficult; he was restless and complained of headache and nausea, and was able to sleep only a few hours during the night. The day before he died he became very restless and was irrational; the pulse was very feeble and irregular, and breathing was increasingly difficult. While there was at times an annoying cough, this was never a prominent symptom. The only alteration in the physical signs noted was an increase in the area of dulness in the lungs and evidences of congestion and edema of the upper lobes.

The red blood cell count was 5,400,000 with normal morphology; the hemoglobin was 90 per cent. The white blood cell count was 17,000; polynuclears, 68 per cent.; lymphocytes, 30 per cent.; basophiles, 2 per cent.

[1] The patient had been suspected of illuminating gas poisoning.

At autopsy, which was done after embalming with a fluid containing formaldehyde, the important gross lesions found were as follows:

1. An irregular cavity with sharply defined walls in the corpus striatum on each side of the brain, containing a clear colorless fluid.

2. A moderately dense lobular pneumonia in the lower and posterior portions of the lungs on both sides.

The liver and kidneys showed nothing abnormal. The heart was dilated and looked pale and fatty.

The microscopic examination of the tissues was not at all interfered with by the previous embalming, the organs being in excellent condition and thoroughly hardened.

The lesion in the brain was of special interest, inasmuch as the patient had had a severe accident about a year before his death. Yet the examination of the tissues involved did not permit of a connection between this lesion and the accident for the following reasons: (1) The cavity contained clear watery fluid, which was not blood-stained. Such a fluid would be seen only in either a congenital or a parasitic cyst of the brain, and such a lesion would not in all probability be symmetrical. (2) The walls of the cavity were perfectly sharp. Microscopical sections showed that the individual brain cells along the walls were perfectly preserved, and that small capillary vessels had been torn across, the ends still remaining open. There was not the slightest evidence of an inflammatory reaction or the formation of a membrane. It is probable, therefore, that this tear was formed post mortem by the injection at high pressure of the embalming fluid. That this is possible was proved by some experiments on human cadavers, in which similar artefacts were induced. The vessels may have been weakened by the action of the poison, especially as Tomellini[1] has shown that in acute nitrite poisoning small hemorrhages can be found in the organs, usually confined, however, to the stomach, intestine, and liver. As stated above, small quantities of nitrous acid may be formed when nitrogen tetroxide comes in contact with moisture. Such nitrous acid would naturally combine with the

[1] Beitr. z. path. Anat. (Ziegler's), 1905, xxxviii, 395.

free alkali in the tissues and blood and circulate as sodium nitrite. This might be the cause also of the very soft and rapid pulse occasionally seen in these cases of poisoning, and suggests an explanation for the very dark color of the blood noted in almost all cases of this form of intoxication, it being well known that nitrites form methemoglobin on contact with blood. The amount, however, is, as previously stated, usually too small to give a characteristic spectrum.

The liver and kidneys showed practically no changes on microscopic examination. A large number of sections from the liver showed a very few small necroses and a little fatty degeneration. The kidneys also were in good condition with only a slight cloudy swelling of the tubular epithelium and some congestion of the tufts in the capsules and of the intertubular vessels; but there were no casts in the tubules and no evidences of interstitial nephritis.

The heart muscle showed a small amount of fat infiltration, but was otherwise normal.

The interesting lesions were those in the lungs. As stated above, there was a lobular pneumonia chiefly in the lower lobes. Between the areas of consolidation there was a very marked emphysema with absorption of a large number of alveoli so as to form large cavities easily visible to the naked eye, a phenomenon which regularly occurs not only in human beings, but also in experimental animals (Figs. 1 and 2). The mucous membrane of the trachea and bronchi was desquamated over extensive areas (Fig. 3). In some places fragments of the epithelial lining could be found still adhering to the walls or collected in masses in the lumen, with extreme edema of the subepithelial connective tissue. Occasionally a bronchus was found into which had grown a cellular plug largely filling the lumen. About the smaller bronchi were areas of consolidation, the alveoli being filled either with a transparent albuminous mass, or with fibrin containing a few leukocytes, or with desquamated alveolar epithelium (Fig. 4). In some places the epithelium was full of phagocyted blood pigment (Fig. 5). Throughout many alveoli contained red blood corpuscles (Fig. 6). The capillaries in the walls were distended with blood and the walls themselves were very edematous and much thickened. In places there was evidence

of beginning regeneration of the alveolar epithelium, which either lined the alveolus (Fig. 7) in the form of a thin flat layer of cells much more prominent than is seen in a normal lung, or occurred as swollen prominent hemispheric cells protruding into the lumen. Sometimes these cells formed considerable masses or were fused into syncytial bodies (Fig. 8). A true organizing pneumonia could hardly be said to be present. The fibrinous plugs occasionally became very dense and were covered with new epithelium, and in rare instances were penetrated by fibroblasts; but this was not at all a predominant lesion. In other portions of the lung the alveolar structure had entirely disappeared, the lung being quite collapsed and the regenerating epithelium showing as solid syncytial masses or as strands of cells lying in the fairly dense pulmonary tissue (Fig. 9). The upper portions of the lungs were fairly well aërated and showed a moderate emphysema, but no other lesions. The bronchial lymph nodes were edematous and heavily pigmented; but otherwise normal. In the smaller vessels of the lungs there were a number of parietal thrombi; occasionally a thrombus filled the entire vessel; and there was some proliferation of the endothelial lining, showing that these thrombi were undoubtedly antemortem. Similar thromboses can be easily induced in animals by the inhalation of nitrogen tetroxide fumes. Obviously, no cultures could be made from the lung, but a large series of sections were stained by the various methods used for detecting bacteria, and no organisms could be found. The condition was evidently a non-progressive pneumonia due to irritation of the corrosive gases inhaled, and showing a tendency toward repair.

The history and clinical symptoms of the case and the nature of the lesions, which correspond exactly with those described in other cases of nitrogen tetroxide poisoning, and the confirmatory results of animal experimentation which follow, point, it seems to the writer, to the conclusion that death in this case was unquestionably due to the accidental inhalation of this gas.

An examination of the literature of nitrogen tetroxide poisoning shows only a moderate number of carefully studied cases. Most of the earlier ones were insufficiently examined, and in few are there any microscopic reports.

Schubert in 1911 was able to collect 213 cases of poisoning by nitrogen tetroxide, of which 55 were fatal. With very few exceptions all these cases occurred in the last fifteen years, and chiefly in the German Empire. There are no doubt many cases which have never been published for obvious reasons. Concentrated nitric acid is extensively used in the manufacture of gun-cotton, nitroglycerin, smokeless powder, and celluloid, and it is said that many cases of poisoning occur in these factories.

The following reports include only those in which an autopsy was performed.

The most carefully studied cases are the four which were reported from Cologne following the breaking of some carboys of nitric acid in a small room about 12 x 6 x 8 feet. The clinical histories were reported by Savels;[1] the pathologic findings by Loeschcke;[2] and the medico-legal aspects of the cases by Czaplewski[3] and Schubert.[4] While the reports do not wholly agree in minor details the important findings are given so fully that a very satisfactory picture of poisoning of this type is presented. For this reason a full abstract of these cases is given here.

Case I.—B. K. The patient was a man, aged forty-two years. He was cleaning out the room after the accident and remained in it for about twenty minutes, when he felt weak and went home. He vomited and had diarrhea, and some hours after the accident was seized with intense dyspnea, cyanosis, and cardiac weakness. He died in the hospital about five and a half hours after he had left the room in which he was exposed to the vapor. The autopsy showed chiefly emphysema and edema of the lungs. Section of the lung had a violet red color and showed many bright red spots, which were especially well aërated. A very abundant, foamy, pale red fluid exuded from the cut surface. In the bronchi and trachea there was much thin foamy secretion with small amounts of thick mucus. The mucous membrane was a bluish-red color. Microscopically the brain showed no lesions except small perivascular hemorrhages. The kidneys showed intense congestion with some necrosis in the ascending branch of Henle's loop. The lungs showed marked emphysema, with intense congestion. The alveolar epithelium was very largely desquamated and lay in masses in the alveoli. In the alveolar walls and also in the lumen there

[1] Deutsch. med. Wchnschr., 1910, xxxvi, 1754.
[2] Beitr. z. path. Anat. (Ziegler), 1910, xlix, 457.
[3] Vrtljsch. f. gerichtl. Med., 1912, xliii, 356.
[4] Ztschr. f. med. Beamte, 1911, xxiv, 557.

were numerous red cells and abundant leukocytes, and in some regions the walls of the alveoli were covered with a hyaline exudate. The mucous membrane of the bronchi was not altered microscopically. The liver showed nothing specially noteworthy.

Case II.—Sch. Th. The patient, aged forty-one years, had always previously been well. While cleaning out the cellar he noticed no discomfort except irritation in the chest and occasional tendency to cough. After the accident he had a mild headache, some coughing without sputum, and a feeling of weakness. Three hours after the accident he had pain in the chest and a chill, and went to bed, but could not remain there on account of extreme dyspnea, a feeling of pressure on the chest, and violent coughing. He was taken to the hospital, and on examination there was found to be extremely pale and cyanotic. The pupils were dilated, and reacted slowly to light; but otherwise there were no nervous symptoms. His mind was clear. Breathing was rapid and difficult, with marked action of the auxiliary respiratory muscles. Over the lung there were sonorous percussion notes, with fine inspiratory crackles; no coughing; no sputum. The temperature was 101.1° F.; the pulse was rapid, 108, small and soft. The heart sounds were pure. The patient had a venesection of 250 c.c. of blood, which was strikingly dark and tar-like, and coagulated rapidly, but spectroscopically showed only bands of oxyhemoglobin. There was a slight increase in the number of white cells. In spite of oxygen inhalations the patient became rapidly worse; he complained of a feeling of compression of the larynx, of intense thirst, and of frightful dyspnea. The face was covered with sweat, the eyes protruded, and he could scarcely speak; the pulse became more rapid, rising to 140, and the temperature was 101.8° F. He died in coma forty-eight hours after the accident, with signs of edema of the lungs, the final temperature being 102.9° F.

The urine passed during his stay in the hospital was small in amount, highly colored, faintly acid, free from albumin, and contained only 1 per cent. of sugar. The ammonia was somewhat increased; acetone positive; aceto-acetic tests negative.

Autopsy showed the lungs greatly distended, covering the pericardium; they were very heavy. The pleural surface was smooth. Sections showed a large amount of edema and congestion, with a general reddish color of the surface and numerous small granular areas scattered throughout, which were of a bright red color and emphysematous. The mucous membrane of the bronchi, trachea, and pharynx was of a bluish-red color. The bronchial lymph nodes were large and swollen. The brain was intensely congested; otherwise there was no change. The kidneys also were intensely congested, with no other change evident. The liver was pale and yellowish brown, and blackened on the application of ammonium sulphide.

Microscopically there were no changes in the brain. In the lungs the alveoli showed great variations in the dimensions. There were areas

of relatively narrow alveolar spaces filled with exudate, partially fibrinous, partially hyaline, and containing many red and white cells. Between such areas there were large greatly dilated spaces, chiefly without content, apparently due to a traumatic emphysema, as shown by the spaces where the torn walls were hyaline, and thrombosed vessels lay near the site of rupture. The epithelial coating of the alveoli was desquamated; that of the bronchi was present in areas, though showing much degeneration; in other places it was entirely missing. All the vessels of the lung were greatly distended with blood. The spleen showed no special lesion except that there were many phagocytic cells containing blood pigment. The liver showed cloudy swelling with numerous foci of degeneration. At the periphery of these areas of necrosis there was already beginning repair with mitoses in the liver cells. In the kidneys the glomeruli tufts were very much distended, filling the entire capsule. In some parts of the capsule there was a small amount of hyaline exudate with desquamation of the capsular epithelium. The cells of Henle's loop are completely necrotic and in the convoluted tubules there is much yellowish granular pigment. Some of this pigment is contained in the tubular epithelium. Hyaline spherical granules are also found in the lumen of the tubules with an occasional hyaline cast.

Case III.—W. W. Previous to the accident the patient had always been well. On entrance to the hospital he complained of moderate pains in the chest, coughing, and slight dyspnea. On examination he was apparently a healthy man in good condition. The skin of the face was reddish, and the mucous membranes were slightly cyanotic. Breathing was a little rapid, percussion sonorous. All over the lungs there were sibilant rales, with a few moist rales over the lower right chest. The pulse was 108. There was some distention of the abdomen with diffuse tenderness. The stools were thin and yellowish. During the day the patient expectorated some yellowish sputum, and some faintly bronchial breathing appeared over the upper lobe of the right lung; and also in the left lower lobe there was moderate dulness, with many respiratory rales. The temperature rose to 39° C. The blood obtained on venesection was dark and of a bluish color, but spectroscopically showed only oxyhemoglobin. There were no abnormalities in the urine. Two days after the accident the patient's mind was clear; he suffered from fever between 39° and 40° C., with irregular remissions. There was bronchial breathing over the right upper lobe and left lower lobe, and edema over the rest of the lung. The sputum was brownish red, thin, and foamy, and looked like pneumonia sputum, but no pneumococci could be found. Five days after the accident the patient had a moderate delirium. Venesection seemed to improve the general condition, but six days after the accident the heart action became very feeble, the pulse was irregular, and the condition progressively became worse; the dyspnea increased with restlessness and picking of the bedclothes. The patient

died seven days after the accident, with evidences of pneumonia and cardiac failure. At no time did the urine show any important changes.

The diagnosis at autopsy was croupous pneumonia in the upper lobe on the right side and the lower lobe on the left; edema of the lungs; localized necrosis in the liver. The upper lobe of the right lung showed fresh adhesions. Both lungs were very large and heavy. On section the whole right upper lobe was granular, in a state of red hepatization, and absolutely free from air. There were fibrinous plugs in the bronchi. The middle and lower lobes were edematous and contained some areas of pneumonia. The left upper lobe and the upper part of the lower lobe were extremely emphysematous. The lower part of the left lower lobe was largely granular, free from air, and in a state of red hepatization, with a few fibrinous plugs in the bronchi. The trachea and bronchi were filled with large amounts of foamy fluid. The liver was enlarged and intensely congested, and showed on cross-section grayish-red cloudy appearance, with some grayish areas scattered throughout. Both kidneys were very large, the capsules slightly adherent, the markings indistinct. The spleen showed intense congestion.

On microscopic examination of the lungs the alveoli in the pneumonic portion were partly of normal dimensions, partly very greatly dilated and filled with exudate which consisted chiefly of fibrin, but in places of a smooth hyaline material. In this exudate there were found in varying numbers cells chiefly of polynuclear structure. In some regions the staining capacity of the alveolar wall was lost and in these areas the exudate seemed to have spread from one alveolus to another. The leukocytes were especially abundant here. Some of the bloodvessels were thrombosed, but the blood supply of the consolidated areas was slight. The alveolar epithelium was absent over considerable areas. In some places there were isolated epithelial cells with long projections extending over the alveolar wall, evidently a beginning regeneration. The projections came into contact with the nearest epithelial cells, and in this way large areas of alveolar substance had been covered with a few flat cells. In areas where the regeneration had gone farther the cells were thicker and more cubical, though at the periphery of these areas they still retained the flattened form. The cell boundaries were often so obscured as to suggest syncytial structure. Finally, some alveoli were entirely covered with cubical epithelium, occasionally much higher than the normal. No mitoses were observed. The epithelium of the smaller bronchi was still preserved. In the portions of the lung not involved in the pneumonia the alveoli were partly free from exudate and partly contained larger or smaller amounts of fibrin, leukocytes, and red cells. The fibrin in places had undergone hyaline degeneration. The epithelial regeneration in these areas had progressed farther than in the hepatized portions, so that most of the alveoli were covered with a thin flat epithelial layer. No bacteria could be found.

Section of the liver showed areas of necrosis in the centre of practically

all of the acini. The central vein was frequently thrombosed. Polynuclear leukocytes were scattered through the necrotic tissue. The liver cells at the periphery of the acini were large, their nuclei rich in chromatin, and showed mitoses. Pigmentation of the liver cells was slight in amount.

The glomeruli of the kidney were large; the capsules were thin, with moderate desquamation of the capsular epithelium. In the capsules were found finely granular masses of albumin, in places compressing the glomerulus. The epithelium of the convoluted tubules was swollen, and many cells showed imperfect staining qualities. The lumen of the tubules contained granular masses of albumin. In Henle's loop there was extensive necrosis of cells, many of which had fallen off in the lumen. The collecting tubules showed numerous small homogeneous casts composed apparently of masses of tubular epithelium. They stained dark with hematoxylin and black with silver; in other words, they probably contained some phosphate of lime, a condition found chiefly in cases of poisoning with mercuric chloride.

Case IV.—A. S. This patient was not engaged in cleaning up the acid, which had been completed, but as night watchman he had to pass through the cellar every hour. During the day following his night work he complained of pain in the chest and abdomen. When examined he was found to have symptoms of a severe bronchitis, with very rapid and irregular heart. He complained also of dizziness and faintness and vomited a good deal. Twelve days after the accident he was seized suddenly with a cerebral hemorrhage and died three days later. Autopsy showed extensive arteriosclerosis, with an area of red softening about 2 cm. in diameter in the left posterior portion of the internal capsule. The hemorrhage was encapsulated, but had broken through into the ventricle, which was filled with fluid blood. In this case the influence of the nitric oxide fumes was probably entirely secondary, as the lungs showed no lesions, but the coughing and vomiting may have induced the cerebral hemorrhage.

This completes the Cologne series. The following reports, while in the main less complete, are of sufficient importance to warrant their inclusion.

Case V.—This is an exceedingly interesting case reported under the title "Bronchiolitis Fibrosa Obliterans."[1] The patient survived the inhalation of the nitrogen tetroxide for nineteen days, so that the description shows well the nature of the lesions and repair which takes place in a long-continued case. From the microscopic findings given it is evident that the regeneration of the alveolar epithelium was nearly complete, though

[1] Fraenkel, Deutsch. Arch. f. klin. Med., 1902, lxxiii, 484.

the cut shows some alveoli still filled with large cells; but in any case the desquamative lesions of the lungs were less striking than the organization and closure of the bronchi and small vessels with new-formed tissue.

The patient was a laborer, aged twenty-five years, who was previously healthy; he inhaled the fumes from a vessel containing nitric and sulphuric acids with a piece of brass casting. (Such a combination gives nitrogen tetroxide vapors.) Immediately afterward he had a severe attack of coughing, with a feeling of oppression on the chest and a good deal of pain in this region. During the course of the night following he was seized with intense dyspnea and entered the hospital. On admission it was noted that he was intensely cyanotic; temperature, 102° F.; pulse, 112; respiration, 72; blood pressure, 105 mm. There was slight dulness over both lungs posteriorly and coarse and fine crepitant rales all over. The patient complained of a feeling of burning behind the sternum. The sputum was small in quantity, reddish brown, and mucoid. The following day the temperature was normal and the cyanosis and dyspnea diminished. Respiration went down to 60, and the pulse to 108. The rales in the anterior portion of the chest diminished. Two days after the accident the patient coughed up rust-colored balls of sputum, showing very few diplococci. From the third to the seventh day after the accident the temperature rose slightly, and there was subcutaneous emphysema of the anterior thorax between the second and fifth ribs. Eight days after the accident the subcutaneous emphysema disappeared and the patient was in fairly good condition, without symptoms except a few rales in the chest, until four days later when the cyanosis and dyspnea returned. The respirations rose to 60 and the pulse to 120. The condition was not so serious as at the first attack. The rales returned with a change in the percussion note. The sputum was reddish brown and mucoid. The patient died nineteen days after the accident.

At autopsy the heart showed slight hypertrophy of the right side. The lungs were very much dilated, so that their borders touched each other at the level of the second and fourth ribs. A few fibrinous adhesions at the left apex and left lower lobe. On the surface of the lung there were a number of somewhat depressed bluish spots of irregular outline, which contained less air than the rest of the tissue. On section these were edematous. Scattered throughout the lung also were small areas of hepatization. In addition there were numerous small nodules of a transparent gray color looking a good deal like tubercles. The small vessels contained thrombi. The right lung also was voluminous and distended with air. In the middle lobe there was an area of hepatization about the size of a cherry. On the surface were numerous bluish-red spots, on the pleural surface of which were small fibrinous coagula. The cut surface showed many irregular dark red areas, and besides these small grayish-white nodules attached to the smaller bronchi. There was an emphysema of the lung, with numerous areas 2 to 3 mm. in diameter. The smaller arteries showed

thrombi adherent to the walls. The other organs showed nothing but congestion.

Microscopic examination of the lung showed a large number of thrombosed small arteries and the hemorrhagic and edematous areas which Fraenkel is inclined to interpret as small infarcts. In the fine terminal bronchi there was a marked epithelial desquamation, the cells often filling the entire lumen. The larger bronchi also showed considerable loss of epithelium. In the finer branches of the terminal bronchi there was a growth of connective tissue reducing the lumen in many cases to a small slit, covered in part with high cylindrical epithelium of the bronchial type. The remainder of the lung showed either emphysema, edema, or collapse. In the dense portions the alveolar walls were thickened with connective tissue, especially near the bronchioles. Some of the thrombi had undergone complete organization with the formation of connective tissue. There was no report of any bacteriologic examination of the lung tissues.

In a later paper Fraenkel[1] reports three more cases of so-called bronchiolitis obliterans fibrosa acuta, one in a plasterer who inhaled a large amount of lime and other dust, and the second in a man working in a drug store. The history of this latter case was very imperfect and Fraenkel says that it was not possible to exclude the inhalation of some irritating substance as the cause of the disease. In the third case reported no history was obtainable, and the diagnosis was made solely on the clinical symptoms of intense dyspnea, cyanosis, and emphysema. Death occurred on the fourteenth day. Microscopic examination of the tissues showed chiefly obliteration of the bronchi.

The report is not very clear, but apparently all these cases lived for at least two weeks. The writer also observed another case with similar symptoms due to the inhalation of large quantities of dust from chloride of lime. He says, however, that the disease is not always due to the inhalation of irritating gases or powders, and that measles and whooping cough occasionally produce in children a very similar anatomic picture. In ordinary lobar pneumonia such a closure of the bronchi by the ingrowth of connective tissue does not occur or is very limited in extent, even in cases in which resolution is prolonged over weeks.

Case VI.—The patient,[2] aged twenty-three years, a tinner by trade, inhaled the fumes from a mixture of hydrochloric and nitric acids. He had a slight oppression in the chest, but continued at work for nine days, though not feeling well. On the tenth day he had a good deal of dyspnea and entered the hospital. When examined he showed very marked cyanosis, especially of the face. Thoracic movements were limited during respiration, which was rapid and shallow. The pulse was 140, very soft, and

[1] Berl. klin. Wchnschr., 1909, xlvi, 6.
[2] Edens, Deutsch. Arch. f. klin. Med., 1906, lxxx, 598.

irregular. Temperature was 102.2° F. There was dulness over the chest. The patient appeared moribund. The sputum was abundant, yellowish, and lumpy. There were physical signs of emphysema, with many moist rales over the lungs. The next day respiration went to 50, the temperature was about 100.4° F., the cyanosis and dyspnea increased, and the patient died twenty-six days after the exposure to the fumes. At autopsy the lungs did not collapse on opening the thorax. There were small hemorrhages in the pleural surfaces of the lower lobes. On section the lungs were densely sprinkled with small grayish nodules 1 to 2 mm. in diameter, which surrounded the smaller bronchi. The mucous membrane of the larynx, trachea, and smaller bronchi was intensely irritated, and in many places had disappeared. No other lesions were found in the body.

Microscopic examination showed marked inflammatory lesions of the trachea and bronchi with congestion and edema. In the lung there were numerous small chronic pneumonic areas with the formation of granulation tissue. The alveoli at the periphery of the pneumonic areas contained a cellular exudate chiefly composed of desquamated alveolar epithelium, the cells being of large size and often loaded with pigment. Some of the alveoli also contained fibrin. There was marked inflammation of the septa of the alveoli, with edema, fibrinous exudate, and leukocytes; the vessels were greatly distended. Thrombi were not noticed, and bacteria were not found in the lung sections.

This case is particularly interesting because of the long continuance of the disease, showing the latter stages of the process, death usually occurring much earlier in the course of the intoxication.

Case VII.—Paul[1] reports the case of a laborer, aged thirty-two years, who was ordered to clean the deposit out of a lead chamber. This deposit consisted chiefly of lead sulphate mixed with some sulphuric acid, the mixture giving off vapors of some of the nitric oxides. For this reason it was necessary that the workers leave the chamber every few minutes, as the stirring up of the mud set free the fumes. The chamber had been cleaned some two hundred times under exactly the same conditions as on the occasion of the accident. There were two other workers also in the chamber who were not in the least affected. The patient entered the chamber three times, remaining for periods of ten to twelve minutes. About six o'clock he went home without complaining in the slightest. Some hours afterward, however, he was seized with dyspnea and very severe coughing. He attempted to go to work the next morning, but collapsed on reaching the factory. The patient was examined by a physician after his collapse at the factory, and was found to be intensely dyspneic, with paroxysms of coughing. The sputum was brownish red in color, having previously been bright yellow. The lungs showed some dulness over the

[1] Wien. klin. Wchnschr., 1895, viii, 665.

lower lobes, but no bronchial breathing, only fine rales all over. The pulse was 110, very soft and small. Temperature was subnormal. About thirty hours after the exposure he had a severe seizure, with extreme cyanosis, great restlessness, and occasional delirium. He went into coma and died about forty-six hours after exposure to the gases, with symptoms of pulmonary edema.

Autopsy showed intense congestion of the membranes and substance of the brain, with numerous punctate hemorrhages in the substance. The mucous membrane of the pharynx, trachea, and larynx was dark red and covered with sticky mucus. The heart's blood was very dark; the organ was dilated and the muscle was soft. The pleura of the right lung showed a number of small ecchymotic areas about 1 cm. in diameter. On section a large amount of reddish foamy fluid escaped from the lung, which was extremely edematous, with the peripheral portions showing a considerable amount of emphysema. Section of the left lung showed the same, but the pleura was adherent all over the thorax, with old adhesions. The stomach showed a small hemorrhagic erosion at the greater curvature. There was no lesion except intense congestion of the viscera. No microscopic examination was reported.

Case VIII.—Schmieden[1] reported the case of a laborer, aged twenty-four years, who was exposed to nitric tetroxide fumes for one hour following the breaking of a carboy of nitric acid and attempts to stop the action of the acid by the use of sawdust. He noticed only slight dyspnea after finishing the work, and on his return home some cyanosis. During the night the patient was unable to sleep on account of increasing dyspnea and very severe cough. On admission to the hospital he was found to be intensely cyanotic; respirations, 78; breathing chiefly abdominal, with marked movements of the alæ nasi and the sternocleidomastoid and scalenus muscles. Percussion note was tympanitic. Fine rales were heard all over the chest. The sputum was abundant, thin, rusty brown in color, like pneumonic sputum after edema of the lungs supervenes. The pulse was 112; no tension. Blood taken from the ear was brownish black in color and on dilution in water became bright red; spectroscopically there was nothing abnormal. The patient died in coma thirty hours after the inhalation of the acid fumes with symptoms of edema of the lungs.

At autopsy the lungs were extraordinarily congested and infiltrated throughout with bloody edematous fluid. The mucous membrane of the bronchi was congested. The vessels of the lungs were distended with dark red and black thrombi. There was intense congestion of the pial veins and the arteries at the base of the brain. There was a yellowish slough on the mucous membrane of the stomach near the cardia. No microscopic examination was made.

[1] Centralbl. f. klin. Med., 1892, xiii, 209.

Case IX.—Kockel[1] reported the case of an apparently healthy male, aged sixty-five years, who had worked for about one hour in a room in which a large quantity of nitric acid had been spilled. Except for a little coughing and dryness in the throat there were no symptoms until six hours after exposure, when he was seized with very severe dyspnea, coughing, and a feeling of great anxiety. The symptoms increased rapidly with intense cyanosis, and the patient died two hours later. At the autopsy there was congestion of the meninges; in the posterior portion of the external rim of the right lenticular nucleus there was an area of softening the size of a hazel-nut, apparently an old lesion. The heart muscle was soft; the cavities were much dilated and filled with dark fluid blood. The left lung was very voluminous; the tissues were soft and tore easily, and on cut section were very dark grayish red. There was a good deal of edema and very little air in the alveoli. The right lung also was very voluminous; the upper lobe dark grayish red and very much congested, with only a moderate amount of fluid in the alveoli. The mucous membrane of the larynx, trachea, and bronchi was bright red and much swollen. No microscopic examination was reported.

In addition to these reports of fatal cases with complete autopsies, there are a considerable number of reports of fatal cases with partial autopsies, and also of cases of mild types of poisoning, some of which are of sufficient interest to reproduce here.

Orfila[2] reported three cases. In the first case, observed by Desgranges,[3] the fumes were evolved by the breaking of a flask of nitric acid, exposure lasting for about five minutes. The patient then went into the open air and recovered from the sensation of choking. He was very thirsty about four hours later, and twelve hours after exposure was seized with coughing and prostration, and seventeen hours after the accident had an attack of intense dyspnea with cyanosis, pain in the abdomen, convulsive movements and delirium, and died about twenty-seven hours after the inhalation of the gas. There was no autopsy.

In the second case,[4] a healthy man, aged twenty-two years, inhaled a large amount of fumes set free by the breaking of a flask of nitric acid. Some hours afterward he took a walk in order to relieve a sensation of oppression in the chest. About nine hours after the accident intense dyspnea supervened. Forty-eight hours after the gas was inhaled the patient died with typical symptoms. At autopsy the right lung was found to fill the entire

[1] Vrtljschr. f. gerichtl. Med., 1898, xv, 1.
[2] Toxicologie, trans. by Kühn, Band i, p. 124, Leipzig, 1839.
[3] Jour. de méd., vol. viii.
[4] Cherrier, Bull. de la soc. méd. émul., 1823.

half of the thorax; it was solid and edematous, most of the fluid appearing to be dark fluid blood. In the left lung there were large amounts of bloody fluid, but some of the parenchyma was still well aërated. The mucous membrane of the trachea and bronchi was of a bloody red color. There were superficial ulcerations in the cardia and pylorus. The contents of the stomach were sour. The other organs showed no changes.

In the third case,[1] a powerful man, aged thirty-four years, was cleaning copper with nitric acid. After two days, during which time he had inhaled a considerable amount of the fumes of the acid, he was seized with headache, cough, and oppression in the chest. Twenty-four hours later on examination he was found to have intense dyspnea, protruding eyes, purple lips, and frequent cough, with sticky yellow sputum. There were coarse rales over the chest. He died twenty-four hours after the onset of the symptoms. At autopsy the lungs were very voluminous, crepitant, and of normal color. The mucous membrane of the trachea and bronchi was vivid red and much swollen. The bronchi contained much yellow fluid, and a similar fluid could be expressed from the lung tissue on section.

Manouvriez[2] reported several cases, the exposure occurring when a warehouse containing sodium nitrite and other substances caught fire. One of the workmen made several attempts to remove the sacks, and was exposed for a few minutes each time to the vapors of nitrogen tetroxide. After the third attempt he collapsed, and was taken to his home. He complained of thirst and intense dyspnea, with intense pain in the chest, and died about four hours after the exposure. His assistant died with the same symptoms about eight hours after the exposure. Another exposed person suffered from violent vomiting and diarrhea, but was ill for only two days.

Autopsies on the first two cases showed that the blood was black and acid to litmus paper, the latter seeming a rather remarkable condition in the light of our present knowledge of the great acid neutralizing capacity of the blood. There was intense congestion of the bronchi and lungs, which were distended with blood and contained several areas of hemorrhage. Hyperemia of the mucous membrane of the stomach was noted, with congestion of the other organs.

Künne[3] reported briefly eleven cases of intoxication due to the inhalation for only two or three minutes of fumes arising during a fire in a building in which a large number of carboys of nitric acid were stored. In some of the cases no symptoms appeared until six or eight hours afterward; the patients having stood about watching the fire, smoking their pipes, etc., and finally going home to bed and to sleep. They were awakened later by intense dyspnea. Some of the patients vomited, and showed great

[1] Sucquet, Jour. de méd., 1860.
[2] Bull. de l'acad. de méd., Paris, 1897, xxxvii, 3me sér., 306.
[3] Deutsch. med. Wchnschr., 1897, xxiii, 414.

cyanosis, nervous symptoms, and rapid and fatal heart action. There were two fatal cases, but these were not observed by Künne. Seven of the patients ran a mild course, and were discharged nine days after exposure, as cured. Four others were much more severely affected and were not able to return to work for two weeks after the exposure. The only exceptional point was that three of the patients showed albumin in the urine. All the others had the usual symptoms previously described.

Pearse[1] reported the case of a man, aged thirty-five years, who inhaled the fumes of nitrogen tetroxide on the breaking of a carboy of nitric acid. Six hours after the inhalation the patient had pains in the chest and difficulty in swallowing and talking. Eight and a half hours after inhaling the fumes he had an attack of severe dyspnea; respirations, 40; high-pitched respiratory murmurs over bronchi and right lung. The left lung was not involved. Bloody mucus was expectorated. Twenty-four hours after the accident signs of consolidation developed in the right lung, with edema and cyanosis of the lips. The patient became delirious and died twenty-nine hours after inhaling the fumes, of edema of the lungs.

Wood and Stephen[2] reported the case of a chemist who broke a bottle containing about three liters of nitric acid, and spent about half an hour in cleaning up the fluid by means of sawdust and cloth; he was not inconvenienced by the fumes. Eight and a half hours after the accident he began to suffer from intense dyspnea and expectorated large quantities of straw-colored fluid, nearly a liter in amount. Respirations, 62; marked cyanosis and very violent cough on the first day; cough less on the second day; none after the third day. Recovery was slow, the patient remaining in bed for ten days.

Harrington[3] reported nine cases of poisoning by nitrogen tetroxide fumes following the breaking of a carboy containing nitric acid. None of the patients felt any bad effects until five to eight hours after the exposure, when they developed dyspnea, rapid respiration, cough, and in some cases delirium. There were no fatalities.

Lange[4] reported two cases of an organizing bronchitis which do not correspond either in the clinical history or in the general autopsy findings with the type of disease due to inhalation of irritating gases, and are here quoted merely because they are frequently referred to in the literature of the subject. In the first case there was a history of cough for eight days, chills, and headache, the patient entering a hospital and dying on the ninth day of the disease with a pneumonia showing subpleural hemorrhages and numerous gray miliary nodules throughout the lung tissue, which proved to be fine terminal bronchi. Each small nodule was surrounded by about 1 mm. of dark-colored lung tissue. The alveoli lying between these nodules

[1] Albany Med. Ann., 1899, xx, 28.
[2] Australasian Med. Gaz., 1909, xxviii, 25.
[3] Wisconsin Med. Jour., 1903, i, 177.
[4] Deutsch. Arch. f. klin. Med., 1901, lxx, 342.

showed no exudation. In the second case, the patient, aged thirty-two years, had been sick for six months with cough and dyspnea. For four weeks before death he had great discomfort so that he was not able to work. Autopsy showed voluminous lungs, hemorrhagic spots in the pleura, and on the cut surface large numbers of small nodules which looked like miliary tubercles. These grayish nodules were surrounded by a narrow ring of reddish tissue. The lung between these areas was quite normal. The vessels showed no thrombi.

Pott[1] reported an instance in which nitrogen tetroxide fumes were formed by the action of acid phosphate on sodium nitrate, the mixture being a preparation used as a fertilizer. About thirty persons were exposed to the vapors, of whom two died, one in twelve hours and one in forty hours. There was no autopsy in either case. The symptoms were typical as described above. Eight persons were confined to bed for a number of days which very severe dyspnea and cough, the sputum being thick and yellow and containing blood and alveolar epithelium. In the most serious case the patient was confined to bed for eight days, but recovery was complete.

Hall and Cooper[2] reported a case in which a carboy of nitric acid was accidentally broken and the acid spread over the floor, attacking some zinc plates and sawdust, and starting a fire. Twenty people were seriously affected, four of whom died, two on the second day and two several weeks later. Dyspnea was present in 100 per cent. of the cases, cough in 93 per cent., vomiting in 53 per cent. Cough with bloody expectoration persisted in 27 per cent. The patients who recovered were found to be more susceptible to cold than before. Two cases were autopsied. The records are very incomplete; it is stated that in one the lungs were large and voluminous and the bronchi filled with bloody fluid. There was much edema of the lung tissue and a thickening of the bronchial mucosa. The second case, in which death occurred one month after exposure, showed bronchopneumonia, with consolidation of the lung, and microscopically the alveoli were filled with cells and beginning fibrosis.

Bauer[3] reported a case of an aniline factory worker who inhaled nitrogen tetroxide. After a short time he had dyspnea and cough, and he died in two days with pulmonary edema. An autopsy showed acute bronchitis, lobular pneumonia, and edema, with thrombi in the pulmonary vessels.

Animal Experiments. In order to study further the lesions seen in the reported case, a series of experiments were carried out on dogs.

Among those who had made previous studies of acid poisoning

[1] Deutsch. med. Wchnschr., 1884, x, 451. [2] Jour. Amer. Med. Assoc., 1905, xlv, 396.
[3] Original report not accessible. Abstract in Virchow-Hirsch, Jahresbericht, 1895, p. 460.

on animals may be mentioned Lesser,[1] who exposed rabbits and dogs to the vapors given off on warming nitric acid. He showed that only occasionally bronchitis, bronchopneumonia, or edema of the lungs supervened. Even after exposing dogs for weeks to acid vapors he was not able to find any microscopic changes in the lungs. The reason for this is that the acid volatilizes unchanged and condenses in the nasal passages, and while it may corrode the tissues there does not penetrate farther. Practically no nitrogen tetroxide is given off from ordinary nitric acid on warming.

Kockel, Bauer,[2] Gréhaut and Quinquaud,[3] and Eulenberg[4] carried out animal experiments with nitrogen tetroxide. Those of Gréhaut and Quinquaud and Eulenberg are not important here because the animals either died within a few minutes or recovered from the inhalation, and no microscopic examinations were made.

Kockel's[5] animal experiments gave the following results: The blood of the animals dying in an atmosphere of nitrogen tetroxide fumes had a chocolate-brown color, but when the animals had a chance to breathe fresh air for a few minutes after the inhalation of the gas the blood was merely dark in color and not otherwise abnormal. The lungs were usually markedly emphysematous; the color was almost always bright red; and on section there were usually reddish areas and much edema. Extensive hepatization was noted only in the animals killed four or five days after the exposure to the fumes. The mucous membrane of the respiratory passages was congested and edematous. The spleen and kidneys showed no gross lesions. The liver was occasionally intensely congested. In some animals swelling, edema, and ulceration of the mucous membrane of the stomach and intestine was observed. Microscopically the chief lesion in the lungs was intense hyperemia, with hyaline thrombi in the capillaries, a condition also observed by Bauer. Thrombi also were found in the larger vessels, leading to the lungs in some cases. An extensive edema of the lung tissue involving the perivascular and peribronchial connective tissue and also the alveolar walls was quite common. Over areas of

[1] Ztschr. f. physiol. Chem., 1877, i, 165.
[2] Loc. cit. Few details given.
[3] Compt. rend. Soc. de biol., 1884, viii, t. 1, 469.
[4] Vrtljschr. f. gerichtl. Med., 1876, xxv, 209.
[5] Ibid., 1898, xv, 1.

moderate extent in the lungs the alveoli contained serous or fibrinous exudate. In the animals which survived for a number of days there was almost always a bronchopneumonia, the alveoli being filled with red and white cells and desquamated epithelium. Four or five days after the inhalation a considerable pneumonic infiltration was usually present, the alveoli being filled with desquamated epithelium, which not infrequently fused to syncytial-like masses. The parts of the lungs free from edema and exudate were emphysematous. Plugs of epithelium and leukocytes cemented with mucus often filled the smaller bronchi. Multiple focal necroses were occasionally present in the liver.

Spectroscopic examination of the blood showed that the chocolate-brown color observed in the animals dying in an atmosphere of nitrogen tetroxide fumes was due to the formation of hematin. This substance was also observed by Kobert in the urine of a patient, but is not as a rule demonstrable in those patients who have survived exposure to the gases. Probably only very small amounts of this substance are formed in the blood. No morphologic changes in the circulating blood were noted.

The necroses occasionally observed in the mucous membrane of the stomach and intestine were undoubtedly due to the fact that some of the fumes had dissolved in the saliva and been swallowed, causing erosions. The results of the animal experiments, therefore, correspond quite closely with the lesions found in human beings.

My own experiments confirm and extend Kockel's results. A few characteristic protocols are appended. Dogs were selected for the experiments because of the ease with which pneumonia is induced in these animals and because the lungs are voluminous enough to permit of considerable topographic variation in the pneumonic areas.

Dog No. 1. Large powerful animal weighing about 15 kilos; was anesthetized with ether and allowed to fill his lungs four times with fumes of nitrogen tetroxide mixed with about an equal volume of air. The animal revived from the ether and seemed pretty well for some hours, but on the following morning was suffering from severe dyspnea both inspiratory and expiratory. He remained quietly in his cage and refused to eat. He coughed a good deal,

and forty-eight hours later was killed. The lungs showed acute bronchitis, with edema, desquamation of the bronchial epithelium, and a small amount of lobular pneumonia, the alveoli containing large cells, many of them pigmented, and a good deal of fibrin and a few leukocytes. The remainder of the lung was deeply congested and showed a good deal of edema with a marked emphysema especially in the anterior portions. The other organs showed no lesions. Cultures from the lungs were sterile. The condition corresponds to that noted in persons dying soon after inhaling the gas.

Dog No. 3. Terrier, weighing about 10 kilos, was lightly chloroformed and allowed to fill his lungs about twelve times with a mixture of equal volumes of air and nitrogen tetroxide. The animal died about ten minutes later and on removal the lungs were found to be almost solid with edematous bloody fluid. Microscopically the alveoli were filled with a serous edema containing many red cells. No lesions were present in the other organs. A similar condition has been noted in some of the rapidly fatal human cases.

Dog No. 4. Terrier, weighing about 9 kilos, was lightly chloroformed and allowed to fill his lungs three times with a dilute mixture of air and nitrogen tetroxide. It soon recovered but refused to eat, had a good deal of difficulty in breathing, with coarse rales over the chest, and coughed a good deal, raising yellowish frothy mucoid sputum. The animal was killed after five days. The lungs showed extreme emphysema with a scattered lobular pneumonia (Fig. 2) most marked in dependent portions. The bronchi were congested and filled with mucus. There were no other macroscopic lesions. Microscopically the lungs showed extensive lesions; the other organs were normal except for a few focal necroses in the liver. The bronchial mucosa was extremely edematous and congested, but the epithelium was still intact (Fig. 10), the cilia even being present in a few areas. The epithelium of the terminal bronchi was swollen and desquamated (Fig. 11), as was that of the alveoli (Fig. 12). The alveolar walls were thickened and edematous, and the capillaries congested. Emphysematous areas alternated with patches of pneumonia (Fig. 2). There were plugs of epithelium in the terminal bronchi (Fig. 13), some of them composed wholly of cells, others of cells covering a growth of fibrous tissue. This is the lesion described

by Fraenkel as "bronchiolitis fibrosa obliterans." Similar plugs filled some of the alveoli (Fig. 14), others contained solid masses of desquamated cells, others were filled with blood, fibrin, and coagulated serum, still others were lined with unregenerating epithelium. Mitotic figures were rare, though present. A number of the smaller vessels showed thrombi in various stages of organization (Fig. 15). The lesions in the lungs were very irregularly distributed and corresponded very closely in all details with those of Case D., except perhaps in the extent of the emphysema, this lesion being less marked in the dog than in the human material, while the bronchiectasis was more extensive in the animal.

Dog No. 5. Irish terrier, weighing 7 kilos, was etherized and given ten breaths of very dilute nitrogen tetroxide. Nineteen days later the dog still had a cough, but otherwise seemed well. It was then given four deep breaths of dilute nitrogen tetroxide, and eighteen days later three inhalations of the same. Six weeks later it was killed. The lungs seemed normal in the gross, and microscopically it could not be determined that there were any changes; possibly the lungs were slightly more emphysematous than those of a normal dog, but repair was extraordinarily complete.

Dog No. 6. Fox terrier, weighing about 9.5 kilos, was given under ether anesthesia, six breaths of dilute nitrogen tetroxide and air mixture. The following day the dog was very quiet, did not seem to suffer very much pain, but coughed a good deal and showed intense dyspnea. The second day after he coughed up thin foamy sputum, did not eat, and vomited small quantities of mucus; for six days he coughed continuously and was then killed. On opening the thorax the lungs were found to be covered with a thin layer of fresh fibrin which was especially abundant over patchy areas of deep congestion. These congested areas were scattered irregularly throughout, and were especially abundant near the thin edges of the lobes; they were quite firm to pressure. The remainder of the lung was well aërated. The bronchi were filled with thick mucus; the mucous membrane was congested. The bronchial lymph nodes were not enlarged. The kidneys and other organs appeared normal. The brain showed no hemorrhages nor softening. Microscopically the lungs showed irregular areas of lobular pneumonia

with fibrin, a few leukocytes, and many desquamated alveolar epithelial cells. There was considerable fusion of the alveoli to form large open spaces. The alveolar walls were much thickened and congested. There was beginning repair of the epithelium in some of the alveoli. The kidneys and liver showed no microscopic changes. Cultures from the lung were sterile.

Dog No. 7. Short-haired, female terrier, weighing 9.4 kilos, while under morphine was given three deep breaths of the concentrated gas. The animal was very dyspneic for a few minutes and then became active and apparently suffered no discomfort. Six days afterward it was coughing a good deal. One month later it was apparently entirely well and healthy, and was then put under the influence of morphine and given two exposures to nitrogen tetroxide fumes, about two hours apart. The day following the animal appeared very sick and refused to eat or drink. Rales in throat and difficult breathing. Two days later it was still coughing up a white mucous sputum. The animal was very quiet and refused to eat. Five days later it was killed. The lungs were very voluminous. There were firm sunken areas along the borders of the posterior portions of the lobes. These areas were of a grayish color. The bronchi protruded from the surface of the cut lung and contained a mucopurulent fluid. The solid lung tissue was greenish gray in color. The bronchi in some portions of the lung were very much dilated. The microscopic changes in the lungs were about the same as in Dog 4, but there was much more emphysema and the bronchi were more extensively altered and dilated. The second exposure evidently extended these changes in an already diseased lung.

Dog No. 13. Short-haired terrier, weighing 8.5 kilos. Under morphine the animal was given several deep breaths of well-diluted nitrogen tetroxide. It recovered and at the end of a month was apparently well, but finally began to cough and lose weight, and was killed five weeks after exposure. During the last few days the animal coughed a good deal. At autopsy a lobular bronchopneumonia was found together with the usual emphysema. An atypical pneumococcus was isolated from the pneumonic areas, and the lesion, when examined microscopically, was found to be quite

different from that seen in the other dogs, corresponding to that found after bacterial infections, The alveoli were filled with a richly leukocytic exudate, and bacteria could be demonstrated by appropriate stains. The lesion was evidently a spontaneous bacterial pneumonia developing in a lung weakened by the action of the nitrogen tetroxide fumes. Such a pneumonia is not infrequent in animals upon whom severe operations have been performed.

Prophylaxis. The chief danger of nitrogen tetroxide lies in the fact that a 1 per cent. mixture of the gas with air can be inhaled without inducing coughing or spasm of the larynx, so that the bronchial and pulmonary epithelium is seriously damaged before severe symptoms supervene. This is quite impossible with chlorine, sulphur dioxide, or ammonia, which cannot be inhaled even in a mixture much diluted with air without causing a spasm of the glottis and suffocation.

As the gas is generated by contact of nitric acid with any organic matter, the straw packings and wooden cases in which the acid carboys are inclosed usually start the reaction, the heat evolved often being sufficient to set the woodwork on fire, thus increasing the difficulty of handling the situation. Nitric acid should therefore be stored in an amply ventilated separate building with stone or concrete floor, if possible, and arrangements should be made so that the room can be promptly flooded with water. The handling of the carboys should be placed in the hands of a few skilled workmen who have been instructed as to the dangers of inhaling the fumes arising when the acid is spilled. Sand is the best material for absorbing any acid which may be upset. If it is necessary for the workmen to enter a room in which the acid has been spilled, their mouths and noses should be covered with cloth moistened with very dilute ammonia.

Treatment. There is no satisfactory treatment after the gas has been inhaled. Breathing ammonia vapor has been suggested, but this only adds a second corrosive gas to that already present in the lungs. Oxygen inhalations aid in combating the dyspnea, but do not touch the cause of this symptom which is chiefly due to the edema of the walls of the bronchi. Morphine and stimulants should be given according to the symptoms.

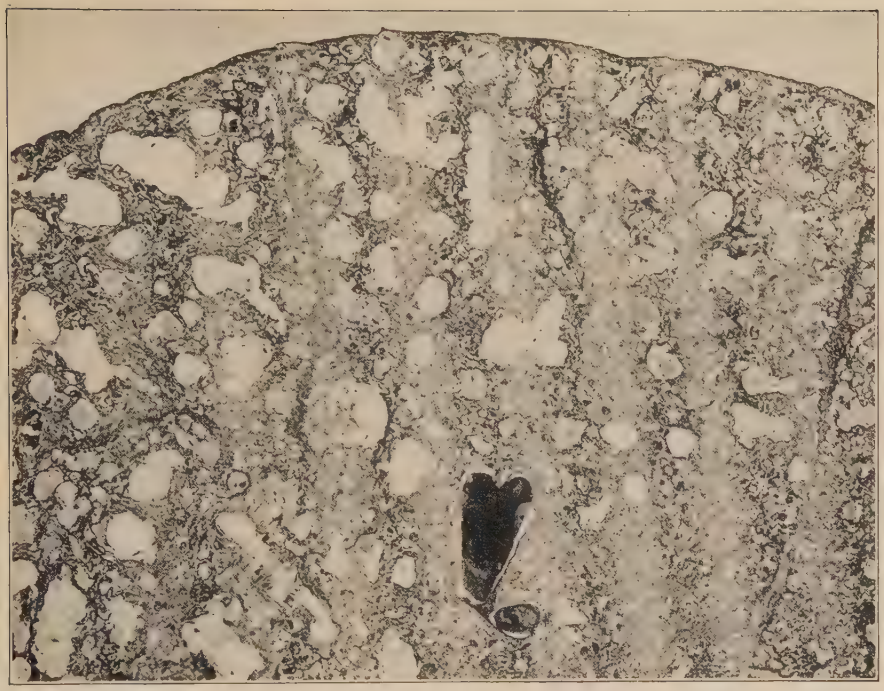

FIG. 1.—Case D. Low power of lung to show irregular distribution of pneumonia and emphysema and thrombi in vessels. × 10.

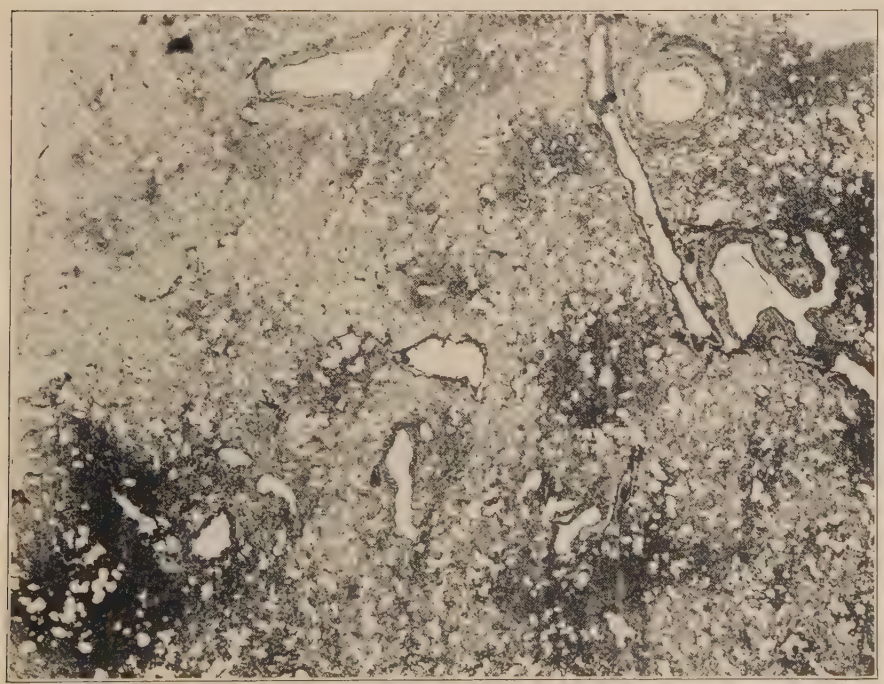

FIG. 2.—Dog 4. Lobular pneumonia with emphysema five days after inhalation of gas. Low power.

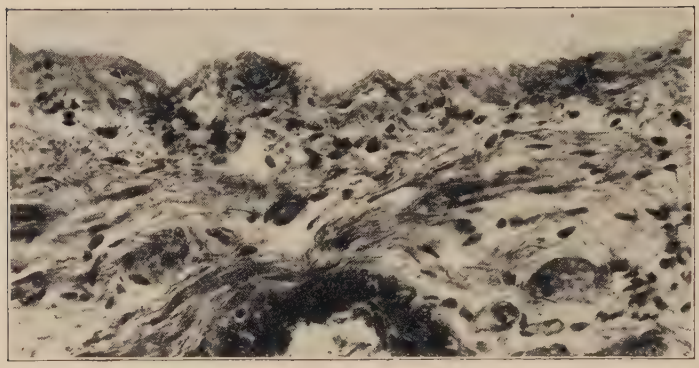

FIG. 3.—Case D. Medium sized bronchus showing edema of wall and loss of epithelium. × 250

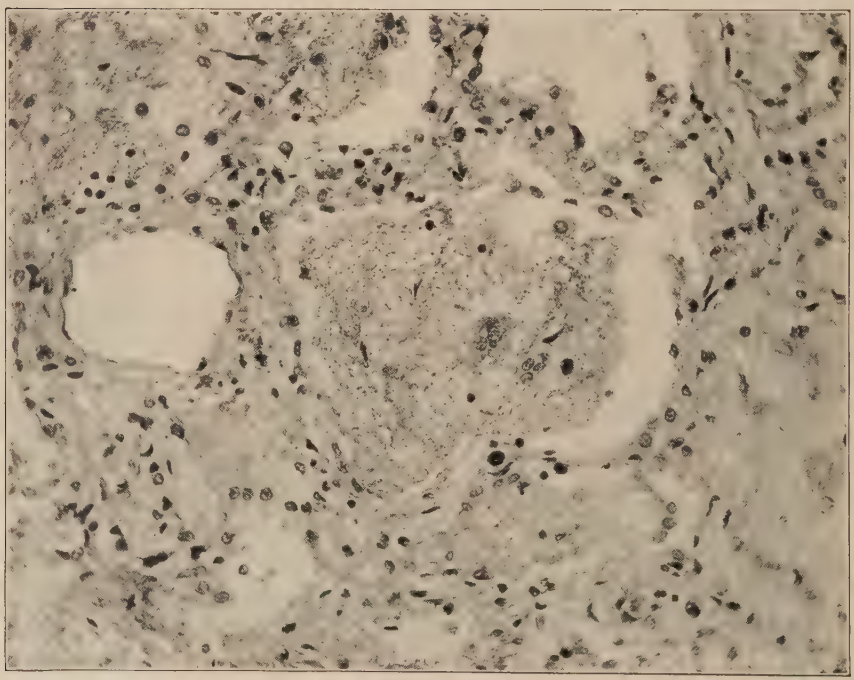

FIG. 4.—Case D. Fibrinous and hyaline exudate. × 250.

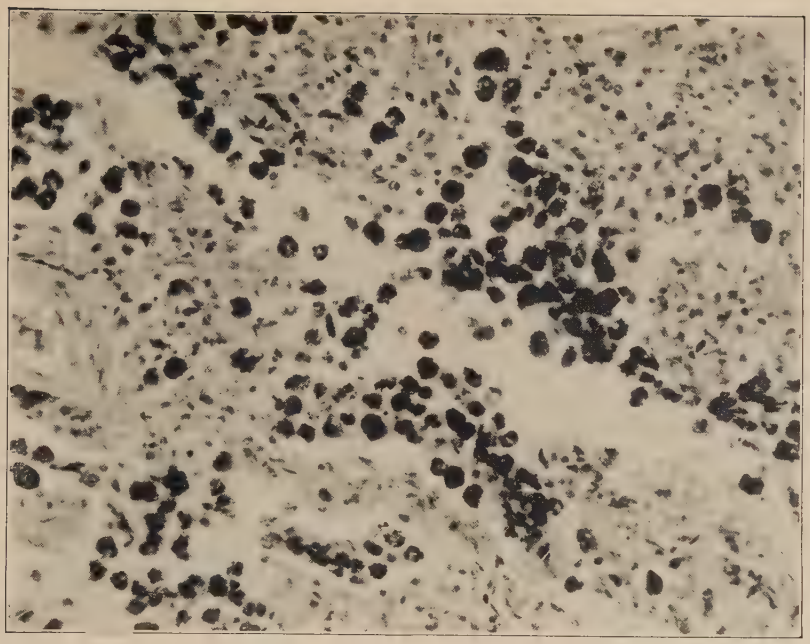

FIG. 5.—Case D. Areas containing chiefly pigmented cells. × 250.

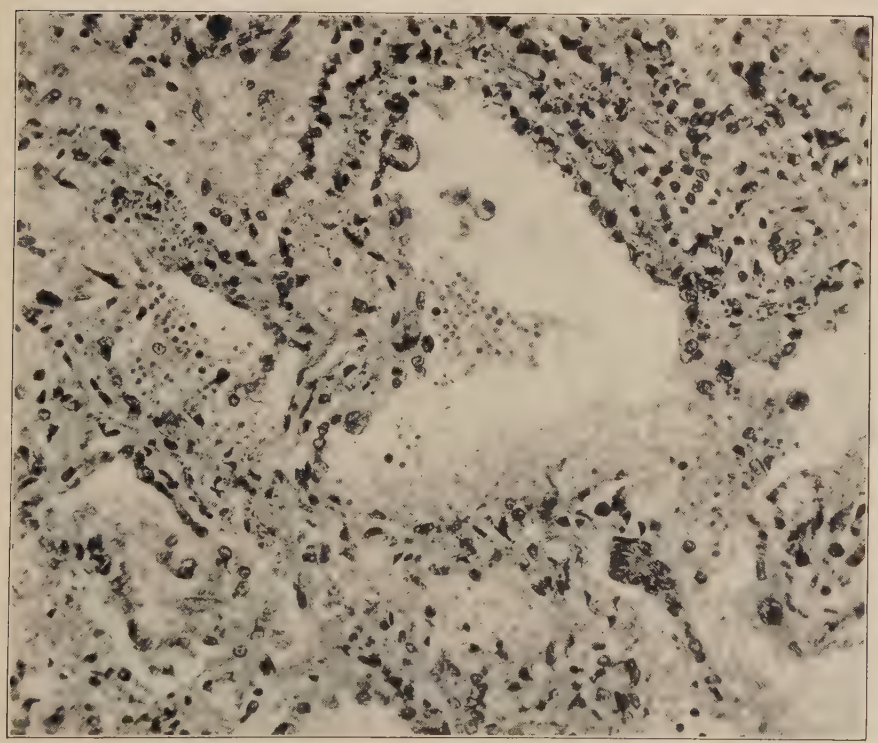

FIG. 6.—Case D. Hemorrhagic portion of lung. × 250.

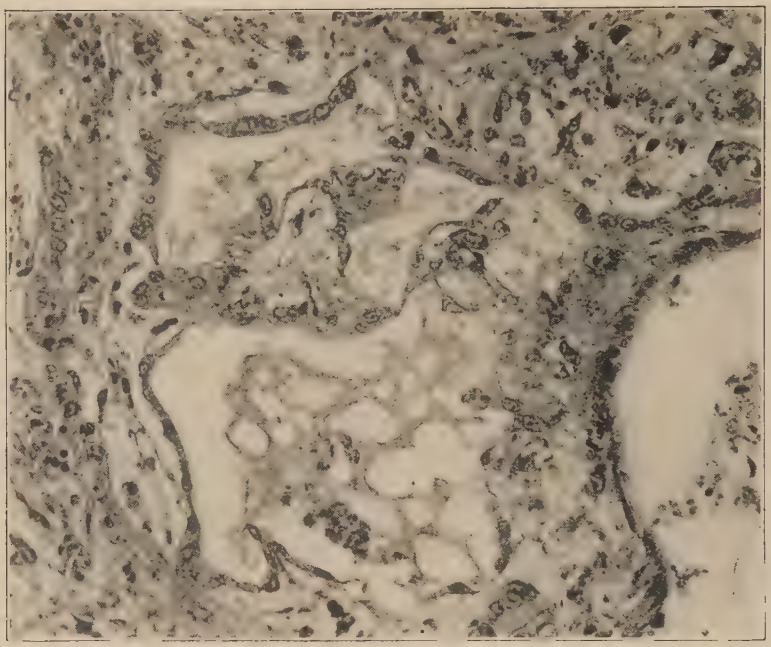

Fig. 7.—Case D. Regeneration of alveolar epithelium. × 250.

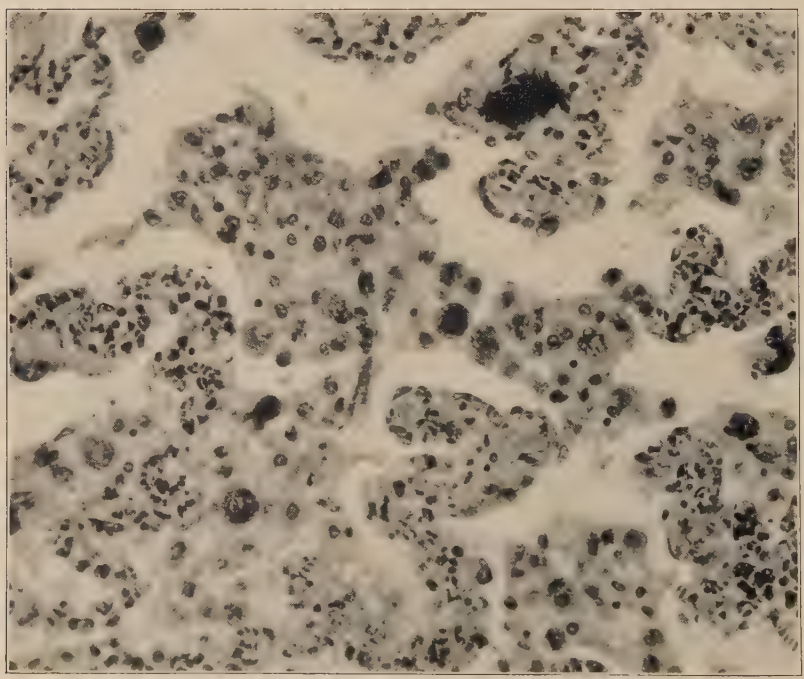

Fig. 8.—Case D. Cellular exudate. × 250.

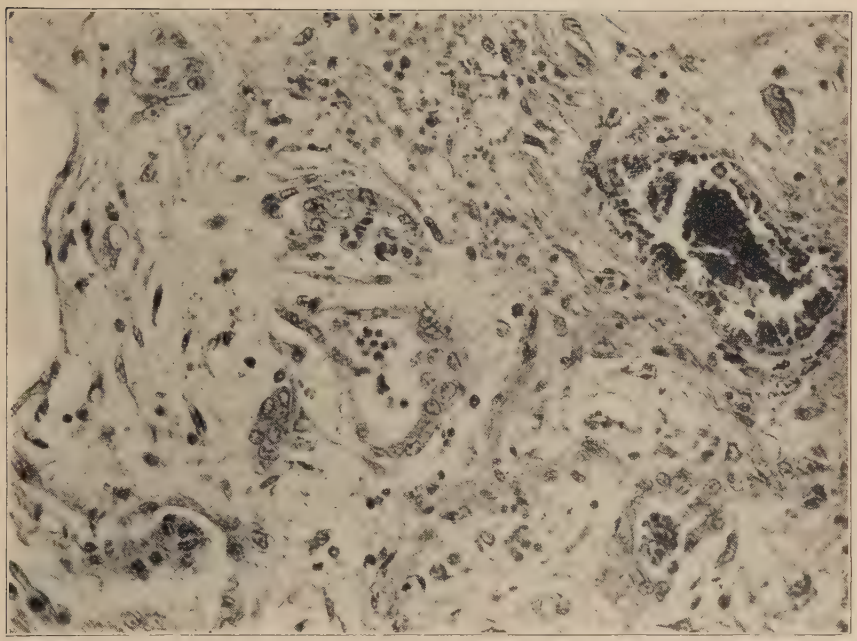

FIG. 9.—Case D. Collapsed and edematous lung with new growth of alveolar epithelium and connective tissue. × 250.

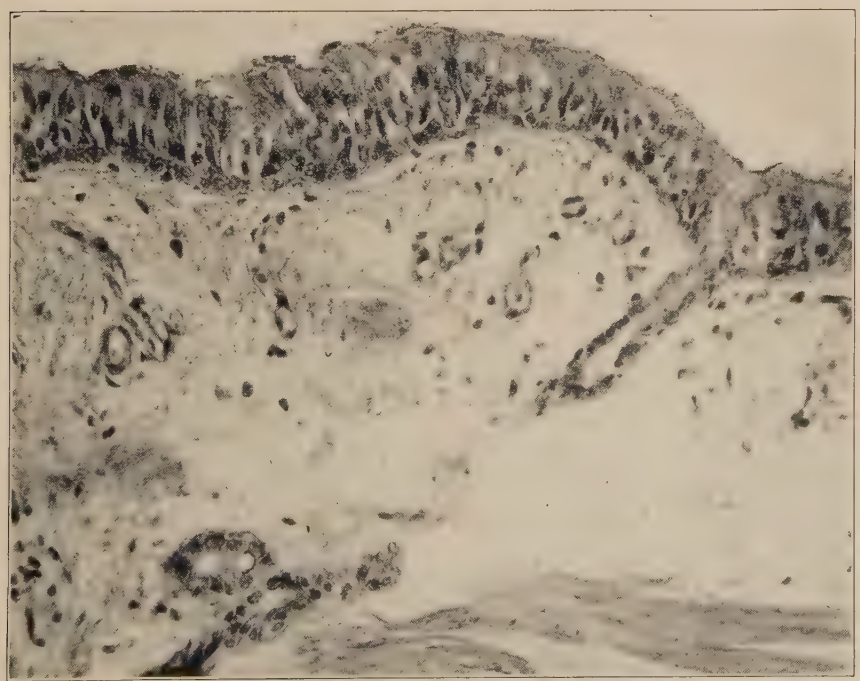

FIG. 10.—Dog 4. Bronchus showing epithelium and cilia still remaining, but marked edema and congestion of submucosa. × 300.

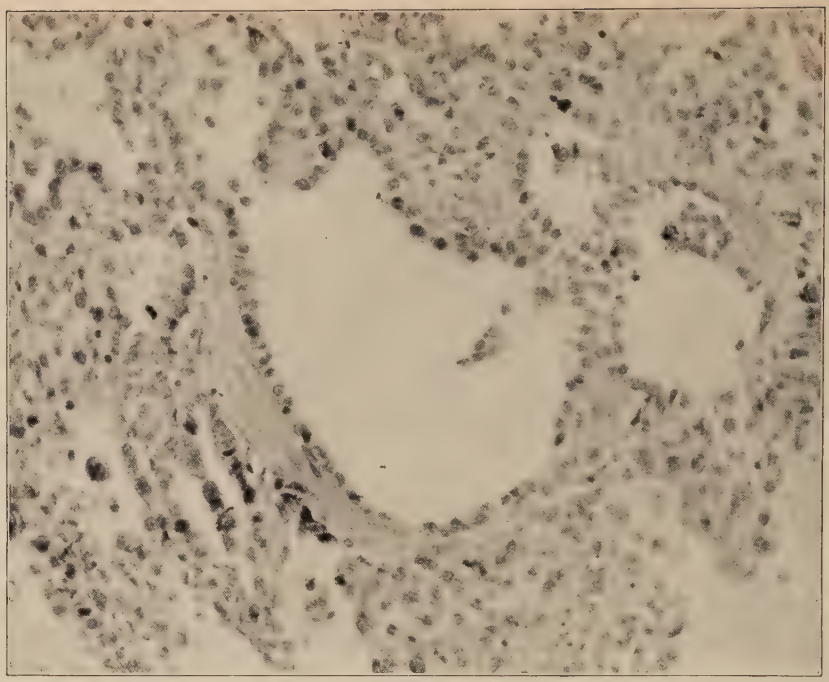

FIG. 11.—Dog 4.—Terminal bronchus and alveoli with swollen and desquamated epithelium. × 300.

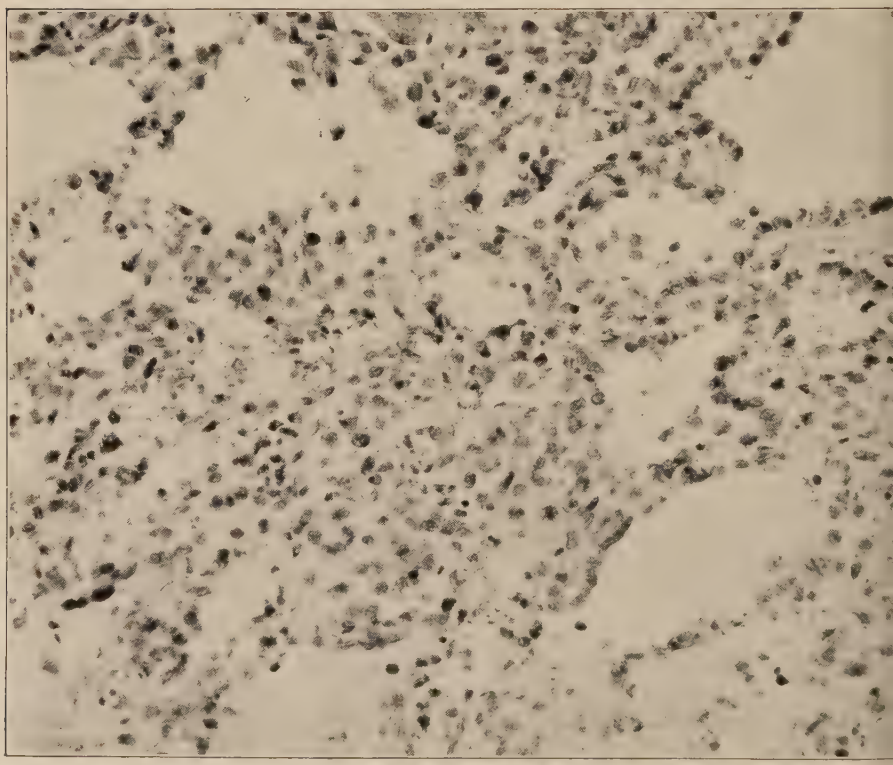

FIG. 12.—Dog 4. Desquamation of alveolar epithelium. × 300.

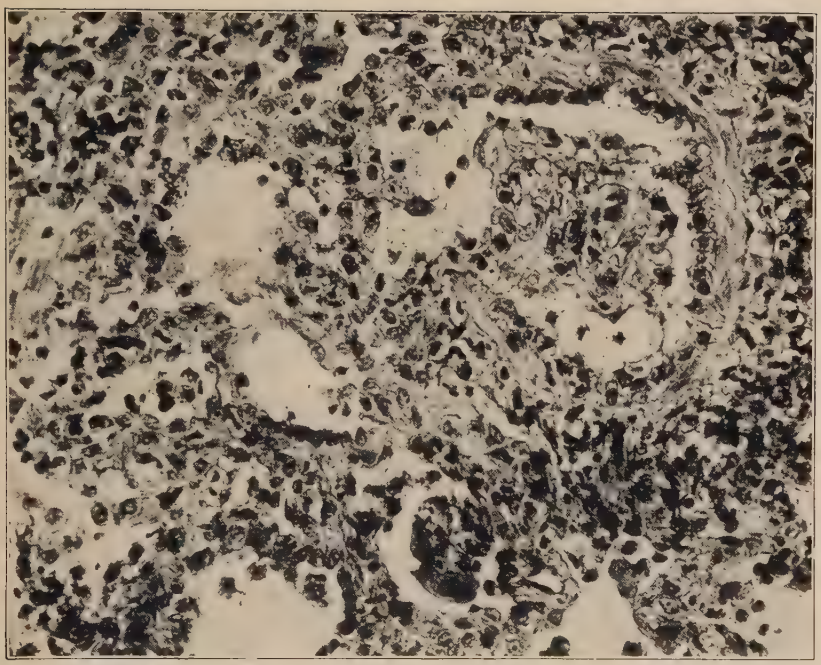

FIG. 13.—Intrabronchial growth of epithelium. × 300.

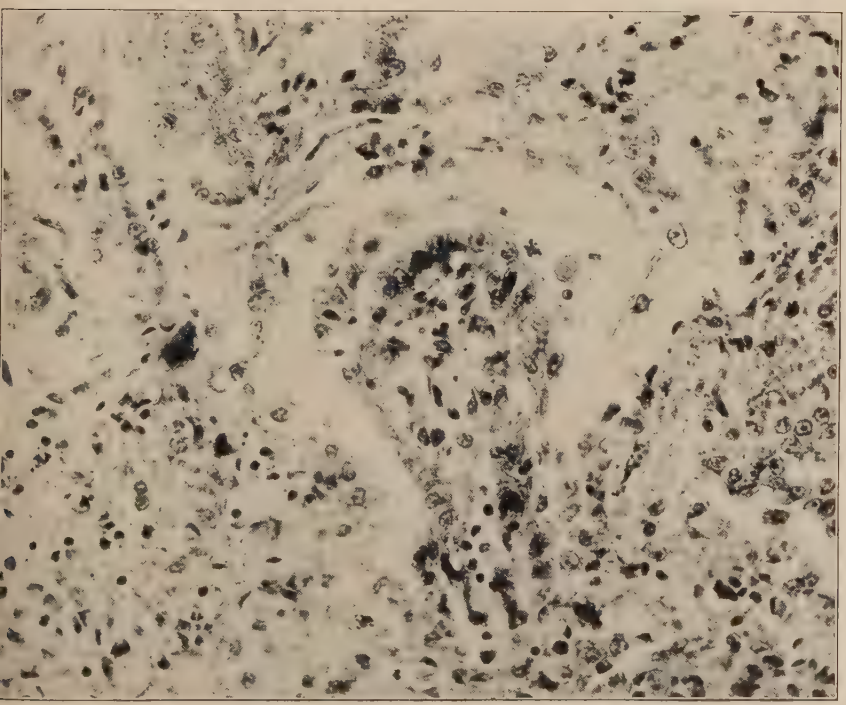

FIG. 14.—Dog 4. Intra-alveolar growth of epithelium. × 300.

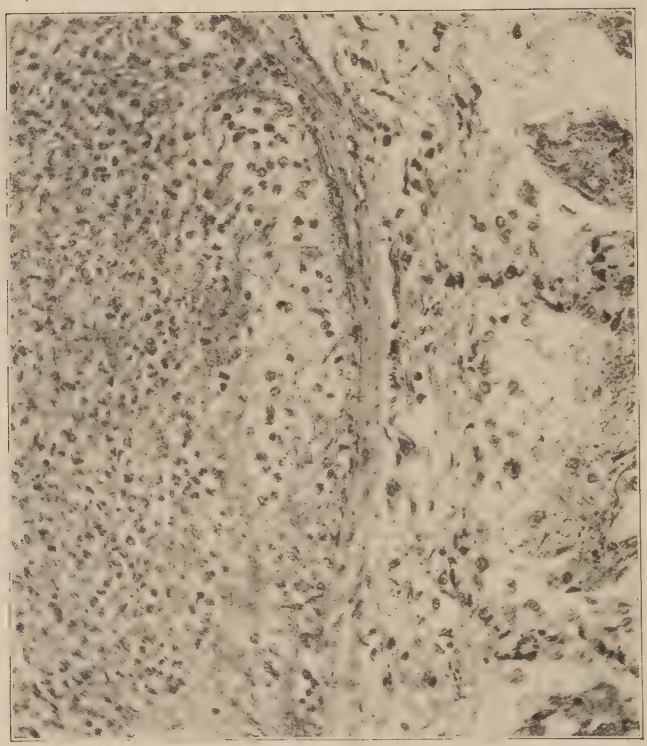

FIG. 15.—Dog 4. Thrombus in a vessel; blood clot to the left; lung tissue to the right. × 300.

CONCLUSIONS. 1. The inhalation of even small quantities of nitrogen tetroxide gives rise to an exceedingly dangerous pulmonary condition with a characteristic lung lesion both in man and in animals.

2. As there is no satisfactory treatment of the condition it is of the utmost importance that careful instruction be given to all factory laborers or laboratory workers who have to handle concentrated nitric acid as to the dangers incurred and the means of avoiding them.

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An excellent description of the symptoms in poisoning by nitrogen tetroxide with a fair bibliography is to be found in Künkel's Handbuch der Toxikologie, Jena, 1901, p. 282. Pott (loc. cit.) gives references to the older cases. Kobert, Lehrbuch d. Intoxikation, 1906, also gives a considerable number of references to the literature, not without the usual inaccuracies. Kockel (loc. cit.) refers to a number of recent cases, and Schubert (loc. cit.) has a fair bibliography and gives important suggestions for prophylaxis. The best bibliography is contained in Witthaus and Becker's System of Legal Medicine, New York, second edition.

THE ABSORPTION OF ANTITOXIN WHEN GIVEN INTRAVENOUSLY AND SUBCUTANEOUSLY WITH SUGGESTIONS AS TO DOSAGE IN CASES OF DIPHTHERIA AND TETANUS

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NEW YORK

This paper is founded upon a series of observations which are given condensed upon two main charts, the one giving the actual antitoxic strength of the blood from hour to hour and day to day in 7 diphtheria cases, each of which had received a single dose of 10,000 units of diphtheria antitoxin subcutaneously, and the other 4 cases of diphtheria in which the same dose of antitoxin was given intravenously.

In the subcutaneous injections it is noticed that in every case the antitoxin content of the blood increased rapidly in amount from the first to the twenty-fourth hour and then, as a rule, more slowly for the next twenty-four to forty-eight hours, and that in none of the cases did the antitoxin content of the blood decrease until after the third day.

In 1 case, a child of fifty pounds, the body actively produced diphtheria antitoxin, so that the content of the blood rose on the fifth day to 60 units. In all other cases only a very little or moderate amount of antitoxin was produced. It is seen that if a single injection is given the blood during every hour of the first twenty-four hours will contain much more antitoxin than if the same amount is divided and given at intervals of eight or twelve hours.

The antitoxin when given intravenously adds to the blood the whole effect immediately and during the first twenty-four hours averages more than five times as much as in cases in which the same dose is given subcutaneously. The antitoxin content of the blood steadily falls after the injection, but not as rapidly as most

people believe. It is evident on the chart that on the fourth day about half of the antitoxic strength still remains. It is seen that, as a rule, the smaller the patient the higher the antitoxin content of the blood. If the individuals did not produce any antitoxin themselves and if the quantity of blood was exactly proportional to their weight and the destruction or disappearance of the antitoxin was similar in all cases, the relative strength in the blood in the different cases would be directly proportional to their weight as it would be simply the question of dilution. These three conditions, however, do not appear uniformly in the different cases, so that while it is true in a broad sense, there are individual exceptions.

Besides the human cases exhibited on the charts the antitoxin content of the blood of two goats is given in a table, one receiving the antitoxin intravenously and the other subcutaneously. Many other animals have been tested with quite similar results.

Intramuscular injections if the serum does not escape from the muscle are absorbed about twice as rapidly as subcutaneous injections of the same size.

THE RESULTS IN TWO GOATS, WEIGHING ABOUT TWENTY POUNDS EACH, RECEIVING 10,000 UNITS OF ANTITOXIN

Hours after injection.	Antitoxin content of blood of goat injected subcutaneously.	Antitoxin content of blood of goat injected intravenously.
3	1 unit	85
6	2 units	75
12	5 units	70
24 (1 day)	9 units	60
48 (2 days)	17 units	35
72 (3 days)	25 units	25
168 (7 days)	8 units	10

An endeavor will now be made to apply to the treatment of tetanus and diphtheria the observations recorded in the charts and table.

The treatment of tetanus with antitoxin has two distinct purposes: (1) The neutralization of the tetanus toxins in so far as that is possible, and (2) the allaying of the symptoms and the keeping alive of the patient.

The neutralization of the poison which is free in the blood can undoubtedly be accomplished in the space of a few moments by

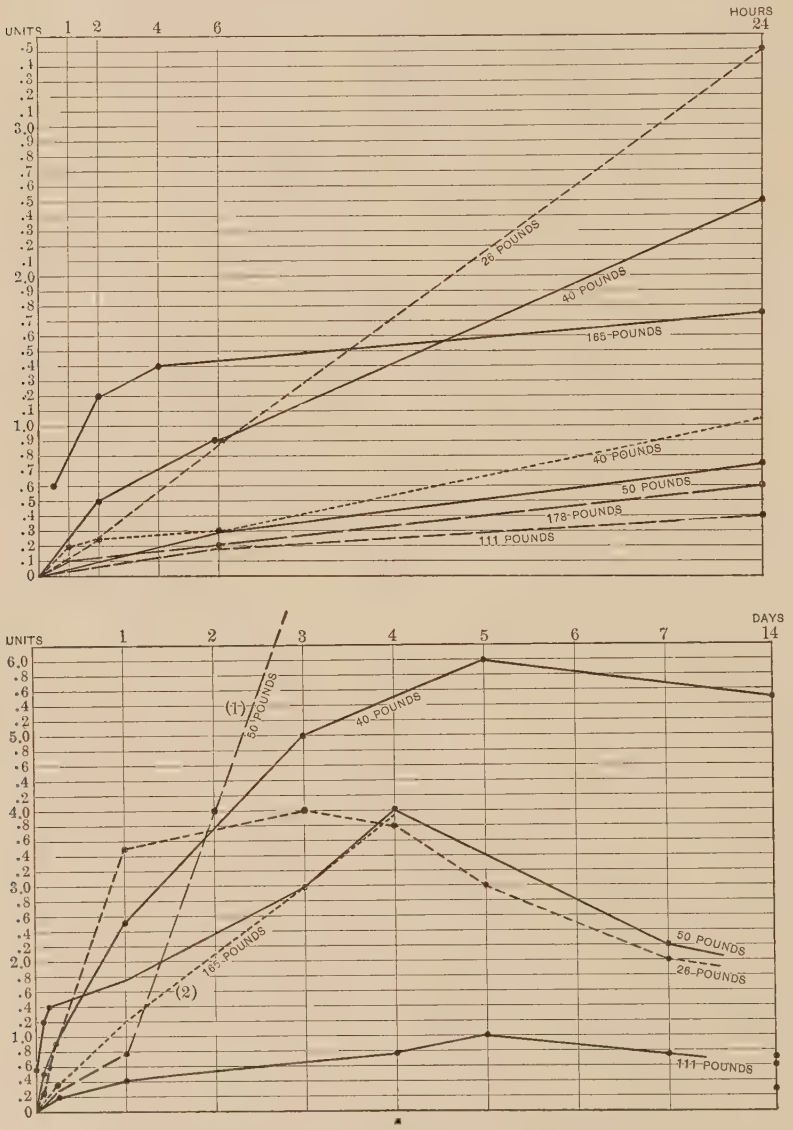

Chart I.—Showing the extent and rapidity of absorption of 10,000 units of antitoxin given subcutaneously. Each line represents the antitoxin content of 1 c.c. of blood at different intervals of time.

an intravenous injection of tetanus antitoxin, but the toxin which is in the lymph and tissue fluids can only be neutralized by the passage of the antitoxin from the capillaries. That which is already thoroughly united to the tissue of the nerves, spinal cord, and brain is probably beyond the influence of the antitoxin. There is, however, apparently an interval of time in which the toxin is in contact with the cells before true union takes place. According to experiments by Kraus, part of this antitoxin will pass out of the cells, if they are surrounded by an antitoxic fluid, just as salts pass through a membrane into salt-free fluids. It is important to clearly understand that in a case of tetanus the greater part

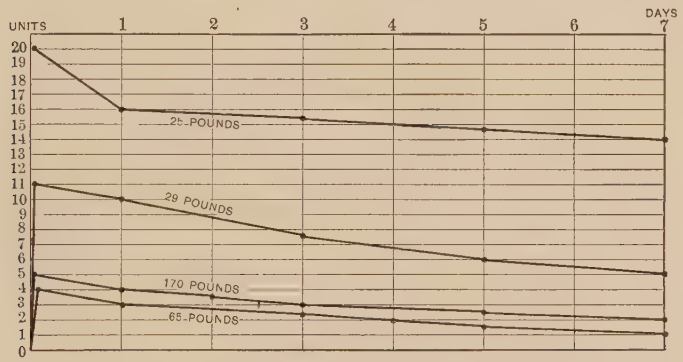

CHART II.—The antitoxic power of human blood after an intravenous injection of 10,000 antitoxic units.

of the toxins elaborated in the infected wound have passed into the lymph vessels of the region involved and then poured into the general blood supply, and from there passed out to the tissue fluids of the body, and there coming in contact with the nerve endings and the cells of the nervous and muscular system have been taken up by them. The first symptoms are the proof that very serious poisoning has already taken place, and that more is impending, for symptoms do not arise until some hours after the contact of the cells with the toxins.

While the nerve tract leading from the wound is somewhat more involved than the rest of the nervous system, still there can be no question that the great mass of the toxin passes into the

blood from the lymph and so gains access to all divisions of the nervous system.

The neutralization of the poison which has not already come in contact with the tissue cells is certainly accomplished when tetanus antitoxin diffuses through the capillary walls to the tissue fluids. As already mentioned it is probable that some of the toxin which has entered the muscle and nerve cells or the nerve endings, may also, for a short space of time, be neutralized and prevented from poisoning. This is believed to take place more rapidly when the fluid outside is strongly antitoxic. The longer the toxin remains in contact with the cells, the greater will be the proportion which has combined with the cell protoplasm so firmly as to be beyond any possible neutralization by antitoxin.

The above facts make it imperative that at the earliest possible moment we give a sufficient dose of antitoxin by some method which will make it possible for it to quickly reach the tissue fluids and the cells bathed by them.

The Method of Injecting Antitoxin. From the fact that tetanus toxin passes up the nerve trunk, or its lymph vessels, which supplies the tissues involved, it was urged that antitoxin be injected directly into the nerve trunk. The direct injection of the nerve trunk can do no harm and probably blocks a small amount of toxin ascending. The fact remains that the major part of the toxin enters the blood and is by it conveyed to all parts of the body.

Since the tissues of the spinal cord and brain are chiefly affected, it has been suggested that the antitoxin be injected into the spinal canal or into the ventricles. Subarachnoid injections do not, however, come into contact with more than the surface of the cord while the brain and deeper portions are equally affected by the toxin. They should be used, if necessary, in addition to and after an intravenous injection.

The question of giving the first dose subcutaneously, intramuscularly, or intravenously is to be decided in favor of the method giving the greatest rapidity of absorption. The full effect of the first injection is needed immediately. Later injections and preventive inoculations can be given equally well subcutaneously.

An intravenous injection throwing the antitoxin directly into the blood current causes, as seen in the charts, an immediate neutralization of all toxin present and within a short time of all toxin in the lymph and cellular fluids. A subcutaneous injection of the same amount is as seen in the charts, not wholly absorbed for three days and the blood does not become sufficiently antitoxic for many hours to allow the passage of much antitoxin to the tissue fluids. The water holding the antitoxin in solution is quickly absorbed from the tissues and the physician does not realize that the antitoxin is held back. As seen in the charts and table at the end of six hours only about 20 per cent. of the antitoxin has been absorbed, and at twenty-four hours, 50 per cent.; forty-eight hours, 75 per cent., and at seventy-two to ninety-six hours, 100 per cent. It is important to remember that the tissue fluids only contain about 1 per cent. of the antitoxin of the blood.

The slowness of absorption of that injected subcutaneously is very evident. The blood current in fact never reaches in antitoxin strength to within 50 per cent. of what it does after an intravenous injection of the same size. Injected into the muscle and retained there the antitoxin is absorbed about two to three times as rapidly as when given subcutaneously, so that the major part is absorbed within twenty-four hours. The rapidity of the intramuscular method, therefore, also falls far short of the intravenous way.

There can be no question, however, that no delay should be permitted, and if for any reason one does not feel able to give it at once intravenously, it should be given subcutaneously. This will soon block any further passage of toxin from the blood.

There is practically no danger in giving it intravenously if ordinary surgical cleanliness is used and the serum is given at a temperature a little above blood heat.

Single or Multiple Injections. The usual method of giving antitoxin is to give an injection every six to twelve hours during the first day and every twelve hours after that time until the symptoms improve. It is difficult after studying the charts to find any reason for the frequent dosage.

As one looks at the charts the conviction becomes strong that

after the first twelve hours following an injection all the toxin in the body not firmly united to the cell substance has been neutralized and that all we have to do further is to keep the blood antitoxic so that any toxin still in the infected area will surely be neutralized. With no further injection the blood remains strongly antitoxic for several days. It would seem that one large intravenous or subcutaneous dose of antitoxin given at the very first possible moment to be followed at intervals of forty-eight hours by moderate-sized subcutaneous injections until the symptoms abated would be all the antitoxin required.

Dose. The dose should be in proportion to the size of the individual, for the final antitoxic strength of the blood depends upon the amount of blood into which the antitoxin is injected. It is far better to give too much than too little. The severity of the case influences rather the prognosis than the dosage.

For an adult of average size an injection of at least 20,000 units should be given. If the expense is not too great and it is available, 30,000 units would be better. As the refined tetanus serum usually contains about 500 units per c.c., the amount of fluid will be about 40 to 75 c.c. For a child of less than fifty pounds, one-half this amount will suffice; for an infant, one-quarter.

If the full amount is not available, give at once whatever quantity is at hand. After an intravenous injection of ten fatal doses of toxin into rabbits a small amount of antitoxin will save if given intravenously within ten minutes. A larger amount, 15,000 units, if given within one hour will save. No amount is of any use after one hour and one-quarter. The first 1000 units given early undoubtedly does the largest amount of good. It is probably wise, although it is hard to see the necessity to give additional doses every forty-eight hours of 5000 units until the symptoms abate.

I have seen a number of cases treated in this manner, and although in some the treatment has had little or no effect, nevertheless, considered as a whole, the results have convinced me that many cases of tetanus are seen early enough to receive great benefit from antitoxin and also that unnecessary delay frequently occurs which makes the antitoxin almost valueless. Literally, every moment of delay is serious.

Diphtheria. The application of these studies to diphtheria though not quite as important as in tetanus is still very interesting. They indicate that the first dose should be sufficient for the case, and that any further doses should only be given because one has not judged correctly the amount required in the first dose. There is no harm in giving additional doses even if the first dose is sufficient, but there is great harm in relying on later doses to add to the effect of the first dose.

We have watched the results at the Willard Parker Hospital in nearly 100 cases of laryngeal diphtheria in which antitoxin was given intravenously in a single dose of 10,000 units and also an equal number in which it was given subcutaneously. The difference was only slightly in favor of the intravenous injections. In a few malignant pharyngeal cases the intravenous injections seemed to give decidedly better results.

In the intubation cases, while the mortality was nearly as high, the general condition of the patient improved more rapidly after the intravenous injections than the series which received the subcutaneous ones. The presence or absence of pneumonia was usually the deciding factor in these cases.

A consideration of the charts shows that it is foolish to consider the given effects occurring soon after a second subcutaneous injection given within the first twenty-four hours of the first injection as due to it alone, as it really is the further absorption of the antitoxin of the first injection as well as the beginning absorption of the second and third injections.

The dose advised in the very severe toxic cases is 20,000 in adults and 10,000 to 20,000 in children. A repetition of the dose is not necessary during the first forty-eight hours and seldom at a later time. In these cases the antitoxin should be given intravenously, if it is possible. The moderate cases receive a single dose of 10,000 units. This is usually given subcutaneously, although an intravenous injection will produce quicker results. In mild cases 3000 to 5000 units suffice.

FATAL POSTOPERATIVE EMBOLISM

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INTRODUCTION

The plugging of vessels by foreign bodies floating in the blood stream was first brought to the attention of the medical world by Virchow, to whom, indeed, we owe practically the whole theory of embolism.

His studies, made principally from 1846 to 1856, were early confirmed by numerous clinical, experimental, and postmortem observations by others, chief among whom should be mentioned Cohnheim and Cohn. Of the latter's work, published in 1860, Welch[1] remarks: "It is extraordinarily rich in anatomical, experimental, and clinical facts, and it is well for anyone who believes that he has a new observation or opinion concerning embolism to consult it before venturing on publication; a precaution which has evidently been often neglected by writers on the subject." When with Virchow's and Cohn's work we place Cohnheim's *Studies on the Embolic Process,* published in 1872, and Welch's classical review of *Thrombosis and Embolism,* published in 1899, we have listed most of the significant literature on embolism.

It is therefore not with a hope of adding materially to any portion of the doctrine of embolism that I present the following data, but merely to place it on record that it may be used for statistical purposes in surgical prognosis, and as a basis for suggesting anew certain precautionary measures for the prevention of embolism.

[1] Allbutt's System of Medicine, 1899, vol. vii, pp. 155 to 285.

TABLE I.—Showing Total Operations, Deaths, etc., Compared with Deaths from Embolism, St. Mary's Hospital, Mayo Clinic, September 30, 1889, to January 1, 1912.

Number.	Region.	Operations 1889 to 1893.	Deaths from embolism.	Operations 1894.	Deaths from embolism.	Operations 1895.	Deaths from embolism.	Operations 1896.	Deaths from embolism.	Operations 1897.	Deaths from embolism.	Operations 1898.	Deaths from embolism.	Operations 1899.	Deaths from embolism.	Operations 1900.	Deaths from embolism.	Operations 1901.	Deaths from embolism.	Operations 1902.	Deaths from embolism.	Operations 1903.	Deaths from embolism.	Operations 1904.	Deaths from embolism.	Operations 1905.	Deaths from embolism.	Operations 1906.	Deaths from embolism.	Operations 1907.	Deaths from embolism.	Operations 1908.	Deaths from embolism.	Operations 1909.	Deaths from embolism.	Operations 1910.	Deaths from embolism.	Operations 1911.	Deaths from embolism.	Operations Totals.	Deaths from embolism.
1	Vessels	11	..	0	..	2	..	5	..	22	..	22	..	43	..	57	..	61	..	65	..	70	..	87	..	80	..	132	..	129	..	131	1	164	..	159	..	132	1	1372	2
2	Thorax and lungs	0	..	1	..	10	..	1	..	4	..	13	..	12	..	12	..	15	..	16	..	14	..	26	..	21	..	28	..	31	..	36	..	35	..	50	..	52	..	6377	
3	Thyroid	0	..	0	..	0	..	3	..	6	..	4	..	0	..	10	..	3	..	18	..	34	..	31	..	36	..	135	..	247	1	439	..	551	1	702	..	1047	..	3266	2
4	Mouth	38	..	5	..	18	..	25	..	34	..	38	..	20	..	30	..	24	..	36	..	33	..	95	..	147	..	138	..	234	..	252	..	318	..	428	..	358	1	2281	1
5	Stomach and duodenum	9	..	2	..	1	..	4	..	11	..	12	..	16	..	26	..	59	..	77	..	139	..	171	..	217	..	214	1	190	..	232	..	272	..	336	1	463	1	2391	3
6	Gall-bladder and liver	9	..	3	..	10	..	21	..	15	..	20	..	33	..	76	..	107	..	149	..	217	1	308	2	329	..	385	..	444	1	528	2	589	2	654	1	700		4597	9
7	Small intestine	2	..	0	..	7	..	5	..	2	..	4	..	10	..	7	..	14	..	15	..	21	..	18	..	7	..	11	..	35	..	27	..	38	..	67	1	99		389	1
8	Appendix	9	..	10	..	11	..	24	..	43	..	50	..	96	..	183	..	303	1	345	..	404	..	536	..	766	1	928	..	1151	..	1344	..	1334	..	1174	1	1197	1	9908	4
9	Colon and rectum	21	..	46	..	34	..	41	..	62	..	69	..	82	..	90	..	101	..	119	..	97	..	118	..	142	..	196	..	214	2	238	1	260	1	269	1	331		2530	5
10	Hernia	9	..	6	..	17	..	32	..	42	..	43	..	76	..	74	..	128	..	150	..	172	..	206	1	294	..	420	1	556	1	636	2	524	..	594	..	522		4501	5
11	Kidney	4	..	5	..	11	..	9	..	12	..	16	..	22	..	22	..	26	..	34	..	35	..	37	..	50	..	73	..	76	..	85	1	107	..	132	..	144		900	1
12	Urinary bladder	5	..	2	..	4	..	1	..	5	..	5	..	9	..	9	..	4	..	16	..	13	..	9	..	29	..	46	..	17	..	32	..	41	..	46	..	66		359	
13	Prostate	0	..	0	..	0	..	1	..	0	..	0	..	0	..	0	..	0	..	6	..	29	..	27	..	63	..	42	..	67	1	86	..	82	..	87	2	111	1	601	4
14	Breast	18	..	8	..	11	..	14	..	11	..	16	..	28	..	35	..	36	..	41	..	37	..	48	..	84	..	98	..	102	..	148	..	202	..	212		197		1346	
15	Uterus, tubes, and ovaries	58	..	73	..	34	..	112	..	179	..	156	..	303	1	312	..	324	1	287	..	360	..	454	1	514	..	720	..	755	2	663	..	806	..	967	2	916	3	7993	10
	Totals	193	..	161	..	170	..	298	..	448	..	468	..	750	..	943	..	1205	..	1374	..	1675	..	2171	..	2779	..	3566	..	4248	..	4877	..	5323	..	5877		6275		42811	47
	Abdominal hysterectomy	5	..	4	..	13	..	12	..	15	..	31	..	39	..	34	..	31	1	51	..	58	..	79	1	97	..	130	..	175	..	173	..	240	..	257	2	268	1	1712	5
	Vaginal hysterectomy	0	..	0	..	0	..	14	..	8	..	9	..	12	..	17	..	13	..	11	..	17	..	7	..	30	..	49	..	58	..	51	..	41	..	57	..	55	..	449	
	Total abdominal operations	86	..	57	..	111	..	196	..	251	..	322	..	470	..	612	..	841	..	1074	..	1302	..	1788	..	2157	..	2750	..	3215	..	3647	..	5079	..	3990	..	4266	..	32174	
	Total operations	1075	..	537	..	606	..	877	..	783	..	973	..	1644	..	1713	..	2124	..	2420	..	2640	..	3131	..	3836	..	4770	..	5553	..	6451	..	7177	..	8218	..	8745	..	63573	
	Total deaths	15	..	1	..	5	..	6	..	10	..	12	..	13	..	21	..	27	..	32	..	69	..	62	..	64	..	69	..	81	..	86	..	83	..	108	..	100	..	864	

TABLE I.—Showing Total Operations, Deat

Number.	Region.	Operations 1889 to 1893.	Deaths from embolism.	Operations 1894.	Deaths from embolism.	Operations 1895.	Deaths from embolism.	Operations 1896.	Deaths from embolism.	Operations 1897.	Deaths from embolism.	Operations Totals.	Deaths from embolism.
1	Vessels	11	..	0	..	2	..	5	..	2	1	1372	2
2	Thorax and lungs	0	..	1	..	10	..	1	..	2	..	6377	
3	Thyroid	0	..	0	..	0	..	3	..	7	..	3266	2
4	Mouth	38	..	5	..	18	..	25	..	8	1	2281	1
5	Stomach and duodenum	9	..	2	..	1	..	4	..	3	1	2391	3
6	Gall-bladder and liver	9	..	3	..	10	..	21	..	0	..	4597	9
7	Small intestine	2	..	0	..	7	..	5	..	9	..	389	1
8	Appendix	9	..	10	..	11	..	24	..	7	1	9908	4
9	Colon and rectum	21	..	46	..	34	..	41	..	1	..	2530	5
10	Hernia	9	..	6	..	17	..	32	..	2	..	4501	5
11	Kidney	4	..	5	..	11	..	9	..	4	..	900	1
12	Urinary bladder	5	..	2	..	4	..	1	..	5	..	359	
13	Prostate	0	..	0	..	0	..	1	..	1	1	601	4
14	Breast	18	..	8	..	11	..	14	..	7	..	1346	
15	Uterus, tubes, and ovaries	58	..	73	..	34	..	112	..	5	3	7993	10
	Totals	193	..	161	..	170	..	298	..	4	..	42811	47
	Abdominal hysterectomy	5	..	4	..	13	..	12	..	3	1	1712	5
	Vaginal hysterectomy	0	..	0	..	0	..	14	..	5	..	449	
	Total abdominal operations	86	..	57	..	111	..	196	..	2	..	32174	
	Total operations	1075	..	537	..	606	..	877	..	7	..	63573	
	Total deaths	15	..	1	..	5	..	6	..	0	..	864	

ANALYSIS OF CASES

From the opening of St. Mary's Hospital, September 30, 1889, to September 13, 1899, a period of ten years, I find no fatal case of postoperative embolism recorded in the annals of the hospital, and no sudden death which could reasonably be ascribed to such a cause, though during these ten years, over 6000 major operations were performed in the clinic.

From September 13, 1899, to December 31, 1911, 47 fatalities from postoperative cases occurred. During this period of twelve and one-quarter years, approximately 57,000 major operations were performed.

Autopsies were made on 41 of the fatal cases, and the clinical diagnoses were quite positive in the remaining 6 cases. Within the same period it is true that a great many non-fatal cases of embolism were noted clinically with more or less positiveness, but the histories in many of these are too indefinite to warrant their tabulation along with the fatal cases, and a review of them is reserved for a later communication.

The cases have been grouped by years in Table I.

The total number of deaths occurring in the hospital for the period under consideration, from all causes, was 864, of which the fatalities from embolism are approximately 5 per cent. The mortality from embolism based on the 63,573 operations is 0.07 per cent. or 1 death in every 1352 operations. When the cases are grouped according to the anatomical regions on which the preceding operation was done, they are found to be as follows:

		Deaths.	Per cent.
After 1372 operations on bloodvessels		2	0.14
After 3266 operations on the thyroid		2	0.06
After 2281 operations on the mouth		1	0.05
After 2391 operations on the stomach or duodenum		3	0.12
After 4597 operations on the gall-bladder		9	0.19
After 389 operations on the small intestine		1	0.26
After 9908 operations on the appendix		4	0.04
After 2530 operations on the colon and rectum		5	0.20
After 4501 operations on hernia		5	0.11
After 900 operations on the kidney		1	0.11
After 601 operations on the prostate		4	0.66
After 7993 operations on the uterus, tubes, and ovaries		10	0.13
40,729		47	0.12

No fatality from embolism occurred in any of the 1346 operations on the breast, though a large share of these were extensive Halstead amputations. Neither did any fatal embolism follow any of the 449 vaginal hysterectomies, though there was 1 case in every 342 abdominal hysterectomies, that is 5 in 1712 cases.

The following are some of the salient facts shown in Table II:

Twenty-six of our patients were males and 21 females. The youngest was aged twenty-five years, the oldest seventy-two years, and the remaining cases were quite evenly distributed throughout the intervening decades.

Forty-one of the patients—all except 4 of the hernia cases and 2 of the appendix cases—had been from two to thirty-five years subject to some form of severe chronic debilitating disease. Speaking broadly, all these were very sick patients when operated upon, and in the light of our present knowledge, the majority of them were probably the subjects of low-grade bacteriemias.

Nineteen of the fatalities occurred within the first week after operation, 21 more within the second week, 4 in the third week, and 1 each on the twenty-sixth, the thirtieth, and the sixty-fourth days respectively. These latter three patients had all left the hospital, and were well along in convalescence. In general, in marked contrast to the serious pre-operative conditions of these patients, it was noted that they were getting along remarkably well just prior to the occurrence of the fatal embolism. These patients, however, were not kept in bed either a materially greater or a materially less time than were other patients having the same type of operation.

In 36 of our cases the embolism was pulmonary, in 10 cerebral, and in 1 coronary. In 28 of the 41 cases posted, the location of the originating thrombus was found in the field of operation or femoral vein. In 4 cases the emboli were found to have originated, in all probability, in the heart, and in the remaining 9 cases the source was undetermined. Arteriosclerosis was found in 5 cases, chronic myocarditis in 11, chronic nephritis in 14, and chronic hepatitis in 18. In 5 of the cases, thorough postmortem examination failed to show any considerable change in any tissue or organ except those incident to the healing of the wound and to the embolus itself.

43	A1451	23192	ry embolism	Pulmonary embolism			
44	48404	39237	embolism	Cerebral embolism			
45	9802G	.....	embolism	Cerebral embolism			
46	A58996	42967	ry embolism	Pulmonary embolism			
47	A53176	.....	ry embolism	Right pulmonary embolism	7993	10	0.13

SPECIAL INFERENCES FROM ABOVE CASES

With this data before us, what inferences may be drawn therefrom? Why for the first ten years in the history of the hospital, during which time 6000 major operations were performed, were there no recognized deaths from embolism, while since that period, 1 case in every 1213 so terminated? Neither the surgeons, the anesthetists, nor head nurses have been materially changed on the staff in that time, nor yet has their method of procedure been materially varied. The anesthetic has been ether since the foundation of the hospital and always it has been given in the smallest amount possible to maintain anesthesia for only sufficient time to permit the rapid completion of the operation. The only changes coincident with the increase are:

(*a*) In the nature of the operations: During the first ten years the number of operations on the stomach, gall-bladder, lower bowel, and prostate, and of hysterectomies was small enough to come under the limit of probable fatality as measured by that of subsequent years. During the last twelve years a very high percentage of our operations have been on these organs, and it is subsequent to operations on these organs that most of our fatalities have occurred.

(*b*) The condition of the patient coming into the hospital and to the operating table has materially changed since the first decade of the hospital's history. During the first ten years of the clinic a very large proportion of the surgical cases was drawn from the general family practice of the members of the hospital staff and were operated upon before they were *in extremis*. During the last twelve years, however, the surgical material has consisted almost entirely of referred cases, with an ever-increasing percentage of those of the "last resort" type, and it is in this class of cases in which most of the emboli have occurred.

GENERAL CONSIDERATIONS

From a study of our own cases and of the literature of other observers I desire to call attention to the following brief general considerations concerning the subject of postoperative embolism.

1. Following operations, particularly on the bloodvessels, alimentary canal, and genito-urinary organs (both male and female), from 1 to 2 per cent. of all cases give more or less distinct clinical evidence of emboli, above 70 per cent. of which are in the lung. Our own data in this regard has not yet been accurately tabulated, but it does not seem to give as high percentages as that from other clinics.

2. As nearly as can be observed from the incomplete and necessarily inaccurate data at hand, about 10 per cent. of postoperative emboli which give clinical symptoms of diagnostic significance cause sudden death.

3. Where post mortems are made on cases of fatal postoperative embolism, the source of the emboli can be definitely determined as venous thrombosis in about 80 per cent. of the cases, as cardiac thrombosis in 10 per cent. of the cases, while 10 per cent. are scattering or undeterminable.

4. Though there must be more or less formation of venous thrombi at the site of every extensive surgical operation, yet it is probable that the long, loosely formed thrombi from medium-sized veins are those chiefly concerned in embolism, and especially in fatal embolism.

5. When large, loose thrombi are once formed in a resting patient, any unusual exertion or change of position may cause a dislocation of large masses which become dangerous emboli.

6. The most important factors concerned in extensive postoperative thrombosis are as follows:

(*a*) *Injury of the Vascular Walls.* Rupture of the intima by cutting, ligating, or clamping causes a rapid deposit of a fibrinous thrombus which, however, is normally confined to an area close to the injury. Over this the endothelium quickly extends, covering the thrombus within a few days. It is probable that such small terminal thrombi, when endothelial-covered, rarely, if ever, become dislocated and form emboli. There can be no question, however, but that the constantly present small thrombi in injured vessels form a nidus for the subsequent development of large, loose thrombi through the activity of other factors.

(*b*) *Slowing and Stagnation of the Blood Stream.* After operations, the rapidity and volume of the current in the veins is materially lessened for a considerable distance proximal to the first

incoming venous radicles. Furthermore, the patient is usually kept quiet in a recumbent posture, thus reducing the force and rapidity of the heart's action and causing a general slowing of the blood current throughout the entire vascular system, including the heart. When the blood stream is slowed, or when a part of the vascular system is incompletely filled, a disarrangement of the blood cells occurs, the white cells and platelets reaching the periphery of the stream and tending to attach themselves to the vascular walls. In addition to this, in the presence of obstacles or marked expansions, a whirling motion, as pointed out by von Recklinghausen, may be set up, which further tends to the retardation of the blood stream, and to the deposition of its elements as thrombi.

(*c*) *Disintegration of the Corpuscles of the Blood from Toxic Substances.* While such toxic substances are not definitely known, their presence is assumed from their apparent action in the severe secondary anemias and hepatic diseases. It has been suggested that this factor may account for the high percentage of postoperative emboli following operations on the gall-bladder. It has also been suggested that toxic substances reaching the circulation from extensive carcinomas may in this manner cause marked postoperative thrombosis. In this connection, however, we must not forget the rarity of postoperative emboli following extensive operations for mammary carcinomas.

(*d*) *Bacteremia.* That bacteria and their toxins are the chief causes of extensive postoperative thrombosis as well as thrombosis occurring in the course of infectious diseases is now fairly well established. By no means all postoperative thrombi occur in the field of operation. Phlebitis and a resulting thrombus is all too frequent. The last decade has seen a very marked extension of our knowledge of the frequent infection of the blood stream by bacteria. This is particularly so in chronic diseases with local infection. It is readily conceivable that bacteria within the blood stream may have their virulence sufficiently reduced to prevent their setting up a local phlebitis until aided by operative traumatism of the intima, postoperative slowing of the blood current, or perhaps even the effect on the leukocytes of a prolonged general anesthetic. Certain it is that many thrombi, which we were

formerly wont to regard as "marantic," we have now come to know are of infective origin. In this connection the postoperative formation of cardiac thrombi (and therefrom pulmonary or cerebral emboli) on small areas of endocarditis is worthy of note. When a polypoid thrombus has been swept off from the wall of the heart, its remaining ragged base may be overlooked without the most careful search at autopsy. While emboli from such a source are by no means common, the possibility of their occurrence must not be forgotten.

7. The above mentioned factors must determine whatever precautionary measures may be taken for the prevention of postoperative thrombosis and embolism. The following suggest themselves:

(*a*) *The reduction of vascular traumatism to a minimum* at operation by the conservative occlusion of vessels, and the provision of free drainage to prevent later extensive external pressure on vessels.

(*b*) *The encouragement of very early free movement on the part of the patient* as soon as the nature of the operation and danger from hemorrhage will permit, though it must be confessed that the reported results from various clinics of "getting the patient up early" are unconvincing as to the reduction of postoperative embolism. If it can be done early enough to *prevent* the formation of extensive thrombi it would seem to be most desirable. If, on the other hand, the condition of the patient's blood either from anemia or bacteremia is such as to lead to the suspicion that extensive thrombi *may have already been formed* before it is possible to permit free movement on the part of the patient, it would then seem the part of wisdom to keep the patient as quietly as possible in a recumbent position to prevent the dislocation of the already formed thrombi. All of the surgeon's judgment may be needed, and even then be at fault, in thus steering between the Scylla and Charybdis of "getting the patient up early" or "letting him have a long rest in bed." Either may be the worst thing or the best thing for the patient, according to whether extensive thrombi have or have not formed. So far as I know, we have not yet sufficient data on which to base an accurate estimate of the time required in a given case for the formation of extensive postoperative thrombi.

We do know, however, that such large loose thrombi once formed are readily dislocated by relatively slight exertion on the part of the patient.

(*c*) *The preoperative administration of drugs to increase the coagulability of the blood*, as, for example, calcium salts in hepatic disturbances, is of questionable value so far as thrombosis and embolism are concerned. It has not been shown that the presence of calcium salts in the blood renders it less liable to form thromboses, though it may be true that their presence induces the formation of a more dense clot.

(*d*) *Measures looking toward the reduction of bacteremia* are certainly indicated as a preoperative precaution for the prevention of thrombosis and embolism. Where possible the preliminary destruction (as with a cautery) of local foci of infection should be considered. When the invading organism can be isolated and identified a preliminary vaccination is suggested. Indeed, it is probable that in some instances such a preliminary vaccination might prove of material benefit to the patient in avoiding postoperative infections other than those of the vascular system.

DISCUSSION

Dr. William H. Welch: With these fatal cases of large pulmonary emboli it is, of course, well known that Virchow pointed out the frequency of cardiac thrombosis and particularly in the appendix of the right auricle and the apex of the right ventricle the old-fashioned marantic thrombi. The surprising thing to me is that they could be the source of emboli so large as to block up the main division or trunk of the pulmonary artery. The sort of emboli that come from these so-called marantic cardiac thrombi very generally have been rather small emboli. Of course, it is sometimes a most difficult thing to find the source of large emboli, and at times the entire thrombus may be washed out from the vein. If there happens to be a fairly vigorous circulation even a good-sized vein of an extremity may be plugged and give rise to so little in the way of mechanical symptoms that the thrombus could be overlooked. I should like to raise the question whether in some of these cases attributed to emboli from cardiac thrombi it might not be that a large clot was completely washed out

from one of the veins of an extremity. It does not have to be such a very big embolus, because it is well known that it can curve on itself many times and a comparatively thin embolus by folding on itself will completely plug one of the main branches.

Dr. Alfred Stengel: I became interested in the subject of sudden deaths from embolism some years ago when I was called in to see a number of cases in which this occurred in the service of my gynecological colleagues. We were particularly interested in the relation of the heart to the embolic accident. A short time before the period I refer to a report was published from one of the German gynecological clinics in which the frequency of fibroid myocarditis in association with fibroids of the uterus was pointed out, and it happened that some of the deaths and some of the cases of embolism not terminating fatally which I saw were in patients who had been operated on for uterine myomas. The report referred to, which was based upon postmortem studies, showed that the weakened heart occasioned intracardiac thrombosis from which the embolisms took their origin. My own experience, which comprised a number of cases, led me to consider with more care than I had done before the condition of the heart in patients about to be subjected to pelvic operations, and in some instances I kept the patient on a preliminary treatment for some time before operation. The result of such a therapeutic test is, of course, scarcely convincing, though in the cases in which it was practised no accidents occured. The need, however, of considering the heart and perhaps keeping the patient on such preliminary treatment is quite apparent from what has been discovered in the clinical and pathological studies.

Dr. Lewis A. Conner: Chiari, in his Harvey lecture in New York a year or two ago, in discussing postmortem diagnosis, referred to the fact that in these cases of sudden fatal pulmonary embolism, often where one could find no obvious source in the large veins, the cause could be shown to exist in a thrombosis of the veins of the calf, as Dr. Welch suggested. He thought that until these veins were excluded that one could not say that the pulmonary occlusion was primary or that it arose from the heart.

Dr. Wilson: Regarding Professor Welch's suggestion that many of those which we fail to find might have been from the field of operation or thrombosis, that is quite true, but then there were 20 per cent. of these that we did not find. I think that of the 24 cases in which we assumed the emboli came from the heart that we have pretty good evidence —not absolutely certain in every instance. Some of these were large lobular emboli. As to Professor Stengel's remarks concerning fibroid uterus, I may say that we have had four fatal cases in fibroid uterus, but in regard to the condition of the heart I have not the data at hand at this moment.

TWO CASES OF TUMOR OF THE SPINAL CORD.

By THOMAS A. CLAYTOR, M.D.
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While reports of tumor of the spinal cord are much more frequently seen now than they were a few years ago they are still of sufficient rarity to justify their publication.

The following cases which have come under my observation have served to arouse my interest in a condition which, if unrecognized, is almost sure to be fatal, and yet one which, if diagnosticated early enough, may many times be relieved, at least for a time, and in a few instances completely cured.

Tumors of the spinal cord may be divided into two classes, the intra and the extramedullary, according as they are within or without the cord substance.

The more usual intramedullary growths are gummata, gliomata, sarcomata, and tuberculomata. Of these the gummata are probably the most common, while the tubercular growths are the most rare.

Tumors found outside the cord substance are again divided into the intradural and extradural. Those most usually observed are gummata, sarcomata, carcinomata, psammomata, lipomata, fibromata, and hydatids. Osteomata and chondromata have at times also pressed upon the spinal cord from the surrounding bony tissue.

Case I.—G. H. R., aged forty-eight years, German, married, a printer by occupation, was admitted to Garfield Hospital, February 21, 1910.

Previous History. Had always been healthy, one attack of gonorrhea when young, no lues.

History of Present Illness. Four years ago began to have dull aching pain in the left shoulder, which, until July, 1909 (seven months ago), was the only symptom.

About this time the pain spread to the other shoulder and to the spine.

In the fall of 1909 the pains became sharp and spasmodic; occurring when he sat in one position for any length of time or turned his body suddenly, also when at stool, or when he coughed or sneezed, and even sometimes upon swallowing. The spasms of pain gradually increased in frequency so that he was obliged to hold his head in a certain position, *i. e.*, when lying down the head was inclined forward with the chin approaching the chest. Turning the head too far to either side produced a spasm of pain which continued until the head was returned to the above described position. When standing he had more freedom of motion, but was apt to have a sharp steady pain when the head was turned to either side rather than the spasmodic variety. It was an effort to hold the head erect, the shoulders also fell forward, especially the left. Emotion or change of temperature might bring on pain.

In October, 1909, he had entered an institution for treatment after consulting numerous physicians. Here he received electricity and various forms of baths and packs. While taking this treatment he became quite ill with fever and delirium. Strange to say, the pains subsided and did not reappear for three weeks thereafter.

In December, 1909, he was referred to an orthopedic surgeon, who put him in various forms of casts which gave considerable relief, probably by limiting motion. About February 14, 1910, the legs and feet began to swell and he began to become quite weak in the lower extremities. Up to this time the symptoms had been sensory. From now on the motor disability advanced rapidly. On February 21 he had to be catheterized for the first time, though for several weeks there had been at times trouble in starting the urinary flow. About February 10 he began to notice that the rectal control was not good, *i. e.*, he was obliged to respond immediately to the desire to defecate to avoid an accident. There had been no loss of weight.

Result of Examination of the Nervous System, February 22, 1910: Reflexes: Radial and olecranon exaggerated; abdominal absent; cremasteric weak on right, absent on left side; knee jerks exaggerated on both sides, as were the ankle jerks; toe extension more marked on the left.

Sensation: No loss of sensation to wool anywhere. On the left anteriorly pinpricks were felt over C 8 (the eighth cervical segment of the cord) though there was hypesthesia over this area. Loss of sensation to pinpricks from D 1 downward (the first dorsal segment of the cord). Posteriorly from D 4 downward. On the right side anteriorly, lost from D 4 and posteriorly from D 5 downward. Relative hypoesthesia to coldness over same segments. The eighth cervical area was not affected on the right side. No loss of sensation to warmth on the left side. Delayed and diminished sensation to ice over D 1 and D 2.

Vibration test: Definite diminution in sense of vibration in D 1 as against C 7. Could feel sense of vibration over the spinous process of the

seventh cervical which could not be felt in the dorsal region. Diminution of the spacing sense in the third and fifth fingers of the left hand.

Motor symptoms: Lower extremities quite weak, walked with difficulty. Left arm somewhat weaker than the right. Adduction of the fingers much weaker than abduction on the left; this included the thumb and little finger. Movements of all the small muscles of the left hand much weaker than normal, except the abductor of the thumb and the abductor of the fifth finger. Flexion of the thumb was weak.

The more important points were as follows: The long duration of pain, the fact that it might be produced by sneezing or coughing, the attitude of spinal flexion, rigidity, with the suddenness of onset of motor symptoms seemed to indicate root pressure (tumor of the meninges). Pyramidal pressure was shown by loss of cutaneous and exaggeration of deep reflexes. Babinski's sign being more marked on the left, together with other more marked signs of left-sided involvement, suggested that the tumor was on the left side of the cord. Escape of the touch sense show show difficult it is to interrupt conductivity.

Localizing Symptoms: Sensation: The higher level of the loss of sensation to pinpricks on the left in the absence of the Brown-Séquard syndrome, indicated that the lesion might be higher on the left side. That the lesion was as high as D 1 was indicated by complete loss of pain sense over that segment, and that it projected to C 8 was indicated by diminution of pain sense over that segment. Diminution to the sense of vibration indicated the same level, as did the hypoesthesia along the ulnar border of the left arm, and disturbance of spacing sense of the left hand.

Mobility: The same segment was indicated by the weakness of the small hand muscles and relative strength of the abductors of the thumb. The Wassermann reaction was negative. The leukocyte count ran from 9000 to 13,800.

Operation. Performed by Dr. L. H. Reichelderfer, February 23, 1910. The cord was exposed by removal of the laminæ of seventh C and first D. The tumor was seen lying upon the left lateral aspect of the cord, after opening the dura, to which it was attached. It was also adherent to the pia, but could be separated from the latter without injuring it. The operation was done rapidly and skilfully, and the shock was apparently not very great. The pain was not relieved, however, nor were the nervous symptoms, except that the reflexes were no longer exaggerated. Death occurred seven days later. The temperature reached 107.2° F. shortly before death. Microscopic examination showed the tumor to be a fibrosarcoma.

Case II.—J. D., white, male, aged forty-five years. Stone-cutter by occupation. Was admitted to Garfield Hospital, January 16, 1912.

Complaint. Pain and stiffness of the neck. His family history was negative. He stated that he had suffered from typhoid fever and malaria,

and from an attack of inflammatory rheumatism, which began a year before his admission and lasted more than six months. (It seems quite possible that the pain experienced in this attack was really due to the spinal tumor rather than to rheumatism.) He denied any venereal disease.

Present Illness. Four weeks ago he began to have pain in the neck. The onset was gradual. The pain was constant and more severe when he attempted to lie down. He soon was obliged to spend his time sitting in a chair with the head forward and the chin resting on his chest. Any attempt to hold the head erect or turn it to either side caused severe pain in the cervical and upper dorsal region. The pain which at first was confined to a small area on either side of the upper dorsal region became severe in the cervical region and ran down the arms into all the fingers. About February 1, urinary incontinence developed.

Physical Examination. A thick-set, well-nourished man, five feet seven inches in height, and weighing about 190 pounds. The head was held in the median line, well forward by anterior flexion of the upper dorsal and cervical spine, the chin resting on the chest. The neck, which was very short and thick, was buried between the elevated shoulders. The feet and ankles were swollen and edematous. The knee and ankle jerks were greatly exaggerated, ankle clonus was present on both sides; there was some doubt as to the dorsal toe flexion on the left, but it was distinct on the right. The cremasteric and abdominal reflexes were absent on both sides. The wrist jerks were bilaterally absent, the elbow jerks present. The lower right scapular reflex was feeble, hyperactive on the left. Deltoid reflex feebly present on the right side.

Motor Signs. Gait slow and unsteady. Muscles of the lower extremities weak.

Upper Extremities. Unable to oppose thumb and little finger of left hand. Movements slow and weak. Apposition imperfect over third finger. Flexion of left thumb weak. Apposition weaker of the right than of the left thumb. Other movements of the right side all stronger. Flexion, extension, abduction, and adduction of left wrist weaker than of the right, but feeble on both sides. Flexion of both forearms very weak. Extension stronger on the right.

Shoulders. Abduction of both shoulders weak, as was elevation of the arms. Adduction a little stronger. Propulsion also weak. Retropulsion much weaker on the left side. Elevation very strong. Depression very weak on the left. Stronger on the right. Adduction of shoulder-blades quite strong. Contraction of the diaphragm seemed strong.

Neck. On passive motion pain was felt in the upper dorsal region of spine opposite the spines of the scapulæ, especially on the right. (A few days later the pain was felt more in the midcervical region.) Over the upper portion of the neck there was a decided dark red congestion of the skin, suggesting a deep-seated inflammatory condition. Percussion over

the spinous processes caused pain in the lower cervical and upper dorsal regions. (Later the greatest pain was noted in the midcervical region.)

Sensation. No loss of tactile sense anywhere. Some anesthesia over dorsum of right foot. Pain sense apparently lessened as far up as the umbilical region. (Later this could not be satisfactorily demonstrated.) There was no altered sensation anywhere in the upper extremities. No abnormal response to the hot and cold test anywhere, or to vibration. No abnormal condition could be demonstrated about head or neck. There was urinary incontinence.

The points worthy of consideration were the following:[1] The marked weakness of the flexors of the forearm and of the deltoids suggested that the lesion was at least as high as C 5 or C 6. The only shoulder movements retained in any considerable degree were elevation and adduction of the shoulder-blades. The former performed by the trapezius (supply derived from C 2, 3, and 4) and the elevator of the angle of the scapula (supply derived from C 3, 4, and 5). The latter is performed by the rhomboids (supply derived from C 4 and 5) and the trapezius. The apparent atrophy of the infraspinatus and supraspinatus also suggested that the lesion involved C 5 or C 6. The apparent competency of the diaphragm (C 3, 4, and 5) seemed to indicate that one or more of these segments was functionating.

Taking the above motor data—there were no sensory to guide us—it seemed probable that the lesion would be found between C 3 and C 6. The *x*-rays showed nothing abnormal in the vertebræ. The Wassermann and tuberculin tests were negative. The leukocyte count was 7000. The lymphocytes were perhaps slightly relatively increased, being 26 per cent. to 61 per cent. of the polymorphonuclear.

Spinal Fluid. Cell average about 1 to the cubic millimeter. Protein content much increased (strongly positive butyric acid reaction). The temperature was somewhat irregular, ranging between 98° and 100° F., occasionally reaching 101° F. The pulse ranged from 80 to 100. The respiration from 18 to 24 to the minute.

The operation, which was performed by Dr. A. A. Snyder, February 15, 1912, was extremely difficult because of the great size of the neck. The spinal cord was exposed opposite to the fifth and sixth cervical vertebræ, but appeared to be normal, and as the localization was not positive, and as the anesthesia had already lasted more than three hours, it was deemed best not to go farther. The patient never rallied, though he lived for five days in great pain, except when under morphine. The temperature reached 106° F. just before death.

Autopsy. A flat tumor was found pressing upon the anterior surface of the cord opposite the third cervical vertebræ. It seemed to take its origin

[1] It seems as well to leave out of account the motor findings in the hands and forearms which were rather confused.

from the dura, and was firmly attached to the body of the vertebra, which had the appearance of being eroded. It would appear that the cord had been exposed about an inch too low, but careful study of the specimen shows that the needle holes made in the dura for its closure during the operation begin on a level with the lower border of the tumor (possibly due to shrinkage of the tissues). Had a probe been passed upward in the spinal canal the tumor must have been felt. Its removal, however, would have been practically impossible without great injury to the cord or nerve roots.

Microscopic examination of the growth showed it to be gumma of the dura (pachymeningitis cervicalis hypertrophica).

I may have erred in not first trying an antiluetic treatment in spite of two negative Wassermann reactions (one of the spinal fluid and one of the blood), but the man's condition was so critical and he was growing worse so rapidly that I dared not wait longer before attempting operative relief, thinking that even if the suspected growth should prove to be syphilitic it might be removed and then treatment instituted.

I wish to acknowledge my indebtedness to Drs. J. B. Nichols, W. W. Wilkinson, and La Fora for laboratory work done on these cases, and to Dr. T. A. Williams for his skilful and invaluable aid in their clinical study.

The radicular innervation of the muscles was taken from Villger's latest classification as given by Bing (*Compendium of Regional Diagnosis,* 1909).

BISMUTH POISONING: WITH REPORT OF A CASE

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Most of us, I suppose, have considered bismuth one of the most harmless drugs in the Pharmacopœia. In fact, however, poisoning by bismuth (perhaps impure) was recorded by Pott in the eighteenth century, was studied experimentally in the early nineteenth, and was well recognized from the clinical side thirty years ago when Kocher reported 6 cases in detail.

Of the 33 cases which I have been able to collect (including my own), 31 occurred when the drug was introduced into the subcutaneous tissues; only 2 cases of poisoning are on record in which the drug was given by mouth. It is almost insoluble in the juices of the gastro-intestinal tract, and as a rule quickly passes out of that tract. On the other hand, the presence of albuminous substances in the subcutaneous tissues—as when bismuth is injected into a sinus or an abscess cavity, or used as a dressing for extensive burns—permits absorption which may take place slowly and continuously over a considerable period.

If bismuth subnitrate is used in large doses subcutaneously nitrite poisoning may occur. This is an acute and alarming intoxication essentially different from the toxicosis produced by bismuth itself. A number of cases of this type occurred when large doses of the subnitrate were in vogue for *x*-ray work, but since the substitution of the subcarbonate and other salts one hears no more of them. In this paper I shall make no further reference to them, but shall confine myself to the results of true bismuth poisoning.

The toxic symptoms of bismuth, like those of lead and mercury, depend mostly upon the method and channels of its excretion.

It is eliminated by the saliva and oral mucosa, by the gastro-intestinal tract (especially the colon), by the liver, and by the kidneys. In mild cases the kidneys first show the evidence of the metal in a black discoloration of the urine and a black deposit. Doubtless such cases are often overlooked, although they may be accompanied by albuminuria and cylindruria. If the bismuth accumulates still further in the system, it begins to make its appearance whenever the presence of H_2S precipitates it in the lymph channels—as in the mouth and colon—thus producing stasis, necrosis, and ulceration.

A black line appears upon the gums, which is produced precisely as the familiar lead line is produced, and has often been mistaken for it. Then a patchy discoloration occurs in the mucosa adjoining the teeth. Wherever the tongue touches them (as at its top and sides) it is blackened and the labial and buccal mucosa, along the teeth line, is similarly discolored. If the process is mild, there may be no stomatitis, but in most of the severer cases, which are recorded in literature, a severe stomatitis like that produced by mercury soon appears.

Gastro-intestinal symptoms are much less common. Vomiting is occasionally seen. There may be diarrhea or constipation, with cramps like those of lead colic. The colitis is rarely as severe as in mercurialism. At autopsy and experimentally there is practically no bismuth staining of the small intestine where H_2S is not produced.

Most of the bismuth deposits are in the cecum, appendix, and adjoining parts of the colon; the staining gradually fades in its lower portion.

The analogy with plumbism is not carried out as regards paralysis, and though headache and convulsions occasionally occur and hyperemia of the brain and cord is found in some cases post mortem, there is no close parallelism with plumbism from the clinical side.

The circulatory and respiratory system are not affected.

The blood shows no changes.

Why does poisoning occur in some cases and remain absent in others? Aside from obvious differences in dose and duration of exposure to absorption it seems at least possible that (as with mercury) the condition of the kidneys has a notable bearing on

the question. With intact kidneys the system can stand without poisoning (*i. e.*, without stomatitis, colitis, etc.) a larger amount of the metal than if the kidneys are diseased. If very little of the bismuth is excreted by the kidney a larger bulk must come out by the saliva and by the intestine. If the lymph channels are thus blocked by the precipitated bismuth sulphide, stomatitis or colitis results.

The recorded cases are as follows:

Kocher, in 1882 (Volkmann's *Klin. Vorträge*, 1882, No. 224; *Chirurgie*, No. 72, p. 1912), reported 6 cases of poisoning:

Case I.—Arthrotomy for tuberculous knee in a young girl; bismuth was used as dressing. A week after the operation the urine appeared dark and was found to contain bismuth (minimal quantity) with albumin and cellular casts. Ten days after the operation a black line appeared along the margins of the gums, with nausea and anorexia. The bismuth was then omitted and all toxic symptoms quickly and permanently disappeared.

Case II.—Resection of hip in a boy; bismuth dressing. In a few days dark colored urine with albumin, granular and cellular casts led to an examination for bismuth which was positive, though only imponderable traces were found. No other evidences of toxic action. Prompt recovery. (Many similar cases are mentioned as occurring in Kocher's experience.)

Case III.—A man, aged thirty-two years, was operated on for tuberculous glands in the neck and axillæ, March 25, 1882. Bismuth dressing applied. March 28 the teeth were sore, loose, and surrounded by swollen gums faintly blue stained. The mouth burned, and a black discoloration of the teeth and especially of the gum margins appeared. Gradual complete recovery after the omission of bismuth dressing.

Case IV.—Showed similar black line on the gums after bismuth dressing of an extensive operation for breast cancer in a woman, aged forty-six years. There were no other symptoms, but the black line persisted and was still present when Kocher's paper was published.

Case V.—Showed no toxic symptoms between the time of the operation and bismuth dressing, March 25, 1882, and his discharge April 4. When she next presented herself she complained of burning in her mouth, falling out of some already rotten teeth, and a two weeks' diarrhea with cramps and dark green stools. Weakness of the eyes was also troublesome. Symptoms soon after disappeared.

Case VI.—Disarticulation at the shoulder-joint for sarcoma of the humerus in an anemic woman, aged fifty-six years, was done March 14, 1882; bismuth dressing. March 17 colicky pain in the abdomen, diarrhea, great prostration, albuminuria, painful tumor in the region of the right kidney, and dyspnea led to death on March 2[illegible]. Autopsy: The whole intestinal tract showed ulcers, scars and (especially in the colon) black

pigmentation. (There were also bilateral cystic kidneys, with almost no cortex left, cysts of the liver, aneurysm of the splenic artery, terminal pneumonia, and purulent bronchitis.) Sections of the intestinal wall showed that the bismuth in the form of a sulphide was deposited in the lymph spaces so as to demonstrate their course very beautifully.

In animal experiments the bismuth was also found in straight tubules of the kidney.

Case VII.—(Petersen, *Deut. med. Woch.*, June 20, 1883, p. 365). An operation was done July 10, 1882, for (apparently) tubercular disease of the knee-joint in a girl, aged fourteen years, very thin and anemic. Bismuth dressing. Eight to fourteen days after the operation there was anorexia and a stomatitis with salivation, tenderness, and bluish discoloration of the gums spread rapidly through the mouth.

Bismuth poisoning was not at first considered on account of the supposed insolubility of the salt, but later it was noticed there was a blackish discoloration of the inside of the glass in which the urine was kept. This deposit was found to be composed of bismuth. August 4 the patient's tongue became dark colored at the tip and sides. August 8 the uvula, the soft and the hard palate, and the mucous membrane of the cheeks opposite the teeth became similarly discolored. The pigmentation was still present, though less extensive in November, when the patient went home with the wound healed.

Case VIII.—Dalché (Société de Médecine Légale de France, 1887, *Boston Med. Jour.*, April 2, 1887, p. 749) reports a case of severe burns dressed with bismuth subnitrate, September 26, 1886. On October 11 stomatitis and a false membrane appeared on uvula and tonsils. Below this the mucous membrane was blackish ("noirâtre"), and there was also a blackish patch with a false membrane on the lower lip, and later on the buccal mucous membrane and on the gums a black band appeared. Diarrhea and vomiting were severe. No albuminuria. Bismuth was found in the urine and feces. The bismuth administered was analyzed and found to be pure.

Gaucher and Balli (*Soc. Med. des Hôp.*, 1895, vol. 12, third series, p. 773) report 4 cases as follows:

Case IX.—A man, aged fifty-five years, suffering from an extensive chronic varicose ulcer, was treated early in March, 1895, with bismuth ointment. April 7, anorexia and slight soreness of the gums. April 14 a severe stomatitis and purplish black (noire violacée) discoloration of the lips, gums, and buccal mucous membrane. The other patients in the ward thought he had been eating black currants ("cassis"). The bismuth was at once omitted. (Analysis showed it to be pure.) April 16 the generalized blackish staining was gone, but there remained a purplish line along the free margin of the gums. The salivation soon cleared up, but when the patient was last seen eight months later (November 15, 1895) there was still some dotted discoloration (pointillé) along the margin of the gums.

Case X.—A cook, aged thirty-eight years, was treated June 11, 1896, for deep and extensive burns, with powdered subnitrate of bismuth and boric vaseline. Eight to ten teaspoonfuls of bismuth were used at each dressing. July 15 a discoloration "like a lead line" was noticed, together with an erythematous stomatitis and slight fever. Ulcerations and discoloration of the buccal mucous membrane followed. The tongue was enlarged and painful. False membranes appeared at the ulcerated points and salivation was intense. The bismuth was omitted and on analysis proved to be pure. By July 19 the tongue was almost black—jet black points relieved on a dark gray surface. On July 25 this discoloration had become confined to the tip of the tongue. The black line on the gums was unchanged. October 18 the line persisted, though less marked. The other lesions of the leg and mouth were gone, but the patient was greatly weakened by diarrhea and vomiting. October 19, death; no autopsy.

Case XI.—A man, aged forty-seven years, was treated August 22, 1895, for a large raw surface left after a crushing injury to the foot. The use of bismuth dressings was begun October 27. November 2 a black line was noticed along the gum margins. The patient had never been in contact with lead so far as he knew. The bismuth was stopped, but November 12 the line still persisted (outcome of case not reported).

Case XII.—A man, aged fifty-four years, was treated for varicose ulcers with powdered bismuth subnitrate from October 24 to November 20, 1895, when a well-marked black line was found on the gum margins of the front lower teeth. This patient had first noticed sore mouth fifteen days after the bismuth treatment was begun (*i. e.*, after the fourth dressing). Rapid recovery followed omission of the bismuth.

Gaucher summarizes the experience up to 1895 as follows:

1. In mild cases only a gum line appears.

2. In severe cases there is stomatitis and general patchy discoloration, "tattooing," of the mouth.

3. In still severer cases there are ulcerations, general evidence of infection, gastro-enteritis, and nephritis. According to Gaucher the line on the gums is more *violet colored* than in plumbism.

Case XIII.—Cohn (*Therap. Monatsschr.*, August 1896, p. 466). A woman, aged twenty-five years, with bilateral phthisis and gastric irritability, was given in the course of three days about three grams of bismuth subnitrate *by mouth*. There followed immediately a metallic taste in the mouth, anorexia, a "gray line like a lead line" on the free margin of the gums, and a blackish discoloration of parts of the tongue. There was also some ulceration of the buccal mucosa. The patient seems much prostrated. (No report of diarrhea or urinary abnormalities.) The bismuth was omitted and in a fortnight the symptoms had disappeared. The patient had a tape-

worm (which later appeared) and the author questions whether the visitor or some idiosyncrasy of the patient's is responsible for the poisoning.

So far as I know the only other case of bismuth poisoning on record in which the metal was administered by mouth is that reported as Case XVIII in this series. (Cases of nitrate poisoning are of course not referred to here.)

Case XIV—Dreesman (*Münch. med. Woch*, February 5, 1901, p. 238). A powerful man, aged thirty-two years, suffering from an extensive burn of the second and third degree, was treated with a 10 per cent. bismuth salve. Three weeks later a black sediment was seen firmly adherent to the glass vessel containing the patient's urine. *Three weeks after this* stomatitis with a "bluish-green" (blaugrünen)[1] discoloration of the gum margins and alveolar processes was noticed. Later it appeared on the upper and lower surface of the tongue and on the soft palate. Gradual improvement followed the omission of bismuth salve, but some pigmentation was still present six months later.

Case XV.—Mühlig (*Münch. med. Woch.*, April 9, 1901, p. 593). A man, aged twenty-six years, received, December 14, 1899, bismuth subnitrate powder as a dressing for a deep burn of the arms, chest, and neck. January 5, 1900, the mucous membrane of the whole mouth, tongue, gums, and soft palate was discolored bluish gray, with a darker blackish-blue line along the gum margins. There were the usual evidences of stomatitis. No renal or intestinal symptoms. Recovery did not occur until the bismuth was curetted off the granulating surfaces. Soon after February 2, 1900, the mouth was normal.

Case XVI.—Similar treatment to a burn, November 8, 1900. November 20 stomatitis, bluish-black discoloration of the gums, tongue, and soft palate. Urine and feces normal. Curetting off the bismuth was necessary as in the previous case. By January 1, 1901, the mouth was well. (This case, like mine, was at first mistaken for lead poisoning. But chemical analysis showed that the bismuth was pure.)

Case XVII.—Mahne (*Berl. klin. Woch.*, February 27, 1905, p. 232) reports a fatal case of poisoning in a woman, aged thirty-five years, of feeble, constitution, treated for an extensive burn of the second and third degree with 10 per cent. bismuth salve. Nearly one-third of the surface of the body was involved. After three weeks stomatitis appeared, with a blue-black discoloration of the gum borders, the tongue, and the mucous membrane of the mouth. Two days later diarrhea, albuminuria, and profuse cylindruria were noted. Death occurred five weeks after the appearance of the stomatitis.

[1] The color is also described as like that seen after eating huckleberries.

Autopsy showed black staining of the mucous membrane of the whole colon; also "parenchymatous nephritis." The bismuth used was found by analysis to be pure.

Case XVIII.—Prior (*Münch. med. Woch.*, September 24, 1907, p. 1934) treated an infant of two and a half weeks for an intestinal catarrh, ordering a pinch (eine kleine messerspitze) of bismuth subnitrate every three hours. Two days later it was found that the mother had given the child 10 *grams of bismuth* (the whole amount ordered) *within thirty-six hours*. The lips, gums, and oral mucosa were stained an intense bluish black, while the face, buttocks, and extremities had a pale greenish-gray tint. The staining increased in the next few days and then gradually faded. Albuminuria was present for several days. Recovery was complete. (Compare Case XIII.)

Case XIX.—Don (*British Med. Jour.*, November 28, 1908, p. 1604) reports the history of a knee-joint suppuration into which, August 22, 1908, three ounces of a 33 per cent. bismuth salve was injected. September 27 the patient showed stomatitis, and "a bluish-gray line about one-sixteenth inch wide was noticed" (on the gum) "opposite the *lower central incisors*. Later the line extended on both sides of and between the teeth and onto the adjacent lips, tongue, and cheeks." October 15 the bismuth was all scraped out. "The whole under side of the tongue and lips were now quite black." October 20 the discoloration and stomatitis were much less marked. No gastro-intestinal symptoms nor albuminuria were observed.

Case XX.—Eggenberger (*Zentralb. f. Chirurgie*, 1908, No. 44, p. 1309) used bismuth (30 grams) by injection for a tuberculous psoas abscess. Six weeks later there was decline of appetite, nausea, vomiting, and a "mercurial-like" stomatitis on the lips and gums with "dark brown" discolorations and ulcerations. Though the bismuth was washed out, the child had convulsions, became cyanotic, and died in a few days. Diarrhea did not occur. Autopsy showed hyperemia of the brain and cord, punctate hemorrhages in the stomach, ulceration of the gut.

Beck (*New York Med. Jour.*, January 2, 1909, p. 20) in the course of his treatment of sinus cavities with bismuth paste has noticed "in many patients" a bluish border at the margin of the teeth, other conditions remaining normal. In one case (Case XXI) he noted ulceration like that described by Kocher and others. In another (Case XXII), six weeks after the injection of 720 grams of 33 per cent. bismuth paste into an empyema cavity, he noticed "the blue border around the teeth" with albuminuria and "a desquamative nephritis." All symptoms disappeared within a few weeks after the bismuth paste was removed by olive oil and a suction pump.

He records one fatal case (Case XXIII) as follows: In March, 1908, a man, aged fifty-seven years, was given 400 grams of pure bismuth subnitrate in paste for treatment of a tuberculous hip sinus of twelve years' duration. Severe stomatitis with bluish-black discoloration of the mouth and gums, diarrhea, and "desquamative nephritis" soon followed. These symptoms

abated gradually, and the patient resumed his occupations for two months. August 1, 1908, he fell, injured his wrist, and a large abscess with bone necrosis, fever, severe albuminuria, and glycosuria followed, and he died August 10, 1908. Autopsy showed a large amount of bismuth in the interlobular veins and bile capillaries of the liver, spleen, intestinal wall (veins and lymphatics), and a faint trace of it was found by chemical examination in the heart muscle. None in the kidneys.

In his book on *Bismuth Paste in Chronic Suppurations* (C. W. Mosby Co., 1910, p. 196) Beck mentions two further cases of bismuth poisoning.

Case XXIV.—After thirty days of injections of bismuth paste for a tuberculous hip sinus in a man, aged thirty-three years, "blue ulcers of the gums, headache, loss of weight, etc.," appeared. The bismuth was sucked out and recovery followed.

Case XXV.—Ten days after the injection of 16 ounces of 33 per cent. bismuth paste into an empyema sinus there appeared "a bluish discoloration at the margins of the gums and also bluish rings around the follicles of the tonsils." The cavity was washed out and in three weeks the symptoms had gone.

Case XXVI.—Reich (*Beiträge z. klin. Chirurg.*, 1909–10, vol. lxv, p. 184). A man, aged twenty-nine years, was operated and drained for appendix abscess April 24, 1909. A profuse foul discharge continuing, a 30 per cent. bismuth paste injection was given June 6; 25 c.c. was used. Four days later the wound was improving but appetite failing. June 12, vomiting, headache, increased fever, and great prostration. Stomatitis and blackish-brown gum line appeared June 14. Next day slight jaundice, delirium, stupor, general muscular tenderness; later tonic and clonic spasms, tenderness over the nerve trunks, and ulcerations in the mouth. The urine contained 1 per cent. of albumin and many yellow stained granular casts. June 16 a dark livid color of the gums was noticed. Death June 17. At autopsy very little bismuth was found in the pelvic pus cavity. The intestine showed nothing abnormal except pigment of the serous coat of the coils adherent to the walls of the pus cavity. The mucosa was absolutely normal. No bismuth was found in the liver, kidneys, or spleen; there was siderosis throughout (nitrate hemolysis?).

This case is notable on account of the probable involvement of the nervous system. (Hyperemia? See autopsy on Case XX.)

Case XXVII.—Rosenbach (*Berlin. klin. Woch.*, February 15, 1909, p. 299) injected 30 grams of 30 per cent. bismuth paste into a cold abscess cavity in the tibia of a woman, aged twenty-five years, in August 1908. Eleven such injections were given in August and September. After the eighth there appeared ulcerative stomatitis with brownish-black ("braunschwarzen") spots on the oral mucosa and along the gum margins. Headache was complained of, but there were no renal or intestinal signs. The bismuth was removed. December 12 the stomatitis was mostly healed, though a small number of bismuth deposits still showed in the gums.

Case XXVIII.—David and Kauffman (*Jour. Amer. Med. Assoc.*, March 27, 1909, p. 1035) injected, September 8, 1908, 3 ounces of 33 per cent. bismuth paste, and September 28, 6 ounces of the same into a hip sinus in a man, aged twenty-four years. Eleven days after the second injection there appeared a stomatitis which soon became intense. A gradually widening "greenish-blue" line showed on the gum margins and on the margins and tip of the tongue. The left side of the tongue became ulcerated and covered with a dirty blue-black membrane. The fauces and throat showed similar staining. There were headache and marked constipation. The ulcerations were gone in six weeks, but five months later a deep blue line an eighth of an inch wide was still visible at the gum margin on both fronts and backs of the teeth, *especially on the lower jaw*. The buccal mucosa opposite the teeth was also still discolored, and the tongue-tip and lateral margin still showed areas of bluish discoloration *made up of punctate spots slightly larger than a pinpoint.*

Case XXIX.—(David and Kauffman, *loc. cit.*) A man, aged twenty-one years, was given on January 9, 1909, 6 ounces of 33 per cent. bismuth paste by injection for a tuberculous hip abscess. Ten days later stomatitis appeared, and on the gums a greenish-blue discoloration, linear, and about one-tenth of an inch from the teeth, was seen. This line was at first made up of pinpoint spots which later coalesced. Later the line extended over the gums of the lower jaw, involving both labial and dental surfaces, and on the lower lip and the lateral edges of the tongue there was a blue discoloration of the mucosa which seemed to follow the configuration of the adjacent teeth.

February 2 there was vomiting and the stains had darkened and changed to a grayish blue. The fauces and tonsils became pigmented and there was extensive foul ulceration of the whole mouth. The parotids were tender, but not swollen.

At the time of death, twenty-seven days after the injection, the tongue was twice its normal size and ragged blue areas of necrosis were seen on the tongue, cheeks, fauces, and tonsils. The gum line was now almost black. *The upper jaw was never affected as much as the lower.* No mention is made of the condition of the urine.

Natsuoka (*Deutsch. Zeitschr. f. Chir.*, 1909, vol. cii, p. 511) reports 3 cases as follows:

Case XXX.—A boy, aged fifteen years, with psoas abscess and tuberculous spondylitis, was given by injection June 14, 1909, 40 grams of 10 per cent. bismuth salve, and on June 28, 20 grams more. July 2, anorexia, prostration, black spots on the gums, and severe stomatitis appeared. July 27, improvement began to be manifest and he soon left the hospital.

Case XXXI.—A peasant, aged thirty-three years, was injected June 14, 1909, with 80 grams of 10 per cent. bismuth paste for psoas abscess. Twelve days later headache, vertigo, pallor, acute stomatitis, with blackish-blue

("schwarz-bläulich") staining of the mouth, tongue, and gums, *especially on the right side*. The symptoms increased and the patient died July 15.

Case XXXII.—A girl, aged six years, with Pott's disease and spinal abscess, was given 40 grams of 10 per cent. bismuth salve by injection, July 3, 1909. August 16 she complained of weakness and absolute anorexia; acute stomatitis and a black staining of the gums, tongue, and oral mucous membrane were found, *especially marked on the right side of the mouth*. A black line along the gum was also noticed. All these symptoms rapidly increased so that on August 20 the uvula, the hard and soft palate, the gums and tonsils were stained bluish-black. August 21, severe abdominal pains, especially in the epigastrium, obstinate constipation and vomiting. August 28, death.

My own case (Case XXXIII) is as follows:

An upholsterer, aged thirty-nine years, entered the Massachusetts General Hospital, July 1, 1908, for an "abscess of the back with necrosis of a rib." For this he was operated upon a number of times; finally on April 12, 1909, the diagnosis "old empyema" appears for the first time. May 18, 1910, Dr. Samuel Robinson injected $2\frac{1}{2}$ ounces of bismuth in paste, and two weeks later a second injection was given.

One week after this second injection, or about June 8, 1910, the patient began to feel pain and soreness at the roots of his teeth and in his right tonsil, and after a few days the temperature became elevated, running between 100° and 102°.

On examination, June 15, it was noted that on the gum along the bases of the teeth was a solid black line about 1 mm. in width, also a dirty blackish slough on the right tonsil. The next day the old empyema sinus was enlarged and a good deal of oily bismuth mixture evacuated. In the daily dressings thereafter and up to the time of his discharge, June 20, considerable bismuth was evacuated. This bismuth staining of the gums and lips, however, persisted at the time when he was next seen, June 27, 1911.

At that time he also stated that since February, 1911, he had had at intervals attacks of abdominal pain, cramp-like, moderately severe, relieved by soda water, or by movements of the bowels.

Physical examination, June 27, showed a mild degree of stomatitis, and about the base of each tooth many dark spots and streaks along the free margin of the gum, like those seen in lead poisoning. There are also dark slaty colored patches on the inner surfaces of the cheeks corresponding with the line of the teeth. Similar discolorations are seen upon the left tonsil and on the inner surface of the lips. An *x*-ray was taken July 4, and showed that there was still a considerable quantity of bismuth in the right chest.

July 6 it was noted that the urine showed a deposit which upon analysis was found to consist of bismuth. The urine and stools were found to be free from lead. Throughout his stay in the hospital, which he left August 21, 1911, he suffered from colicky pains like those previously referred to,

and his bowels moved two to four times a day. He had no fever; the pulse ranged in the vicinity of 100. Repeated examinations of the blood showed no trace of the basophilic stippling so commonly seen in lead poisoning. Besides a moderate degree of leukocytosis the blood showed nothing abnormal. The urine was observed to be of a sooty color on June 28, and is noted as "slate-colored" on July 10 and 18, "gray" on July 25 and 31, and "black" on August 12. The reaction was always acid, the specific gravity in the neighborhood of 1020; a very slight trace of albumin was always present and a small amount of sugar, which once or twice reached 75 grams a day, but was usually in the neighborhood of 20 grams. Acetone and diacetic acid were absent. No attempt to limit the ingestion of carbohydrates was made as patient was greatly emaciated. The sediment of the urine contained many fine and coarse granular casts and cellular casts. Bismuth was found in the stools as well as in the urine. The preparation of bismuth used was analyzed and found to be pure.

August 12 more pus and bismuth were evacuated from a pocket near the old sinus, after which he gained somewhat in weight and strength. He was not seen after August 21, but we heard of his death on September 17, 1911.

The main features and the 33 cases above summarized are presented in the following table:

TABLE I.

Number of cases included	33
Number of cases resulting fatally (11 days to 5 months)	10
(11, 12, 25, 27 days, 4 weeks, 5 weeks, 2 months, 3 months, 5 months.)	
Period between the injection of bismuth and the appearance of mouth troubles 3 days to 6 weeks	
1 week or less	11 cases
1 week to 1 month	20 cases
More than 1 month	2 cases

	Wound dressing.	Injection.	By mouth.
Bismuth given	18	13	2

Duration of symptoms (except line on gums) 2 days to 6 weeks

TABLE II.—SYMPTOMATOLOGY

	Cases.
Deposit of bismuth in oral mucosa	30
Stomatitis	24
Parotid tenderness	1
Albuminuria	8
Glycosuria	2
Black urine or black sediment due to bismuth	4
Nausea or vomiting	7
Diarrhea	7
Constipation (obstinate)	2
Abdominal colicky pain	4
Prostration	10
Headache	5
Convulsions	2
Paralysis	1
Tenderness over nerve trunks	1

EXPERIMENTAL WORK

The earliest experiments were apparently those of Orfila[1] in 1818, who showed that bismuth subnitrate given by mouth could be recovered from the liver, spleen, stomach wall, and urine. Its excretion in the milk of goats was proved by Henry and Chevallier in 1839. Orfila's animals did not die when the metal was given by mouth, but fatal results followed its subcutaneous use within twenty to forty hours. (This was in all probability nitrite poisoning and not bismuth poisoning.)

In 1869 Rudnew gave 0.06 gram of bismuth subcutaneously and killed his animals. He produced a stomatitis resembling that due to mercury, and recovered bismuth from the saliva and the oral mucosa.

In 1886 Meyer and Steinfeld[2] produced in rabbits, cats, and dogs, about the sixth day after the subcutaneous injection of *B. O.*, anorexia, vomiting, diarrhea, tenesmus, and in dogs also a stomatitis with ulcerations, albuminuria, muscular ataxia, paralysis, and tetanic spasms. Death followed about the thirteenth day. At autopsy, intense black pigmentation was found in rabbits, cats, and dogs, especially about the cecum. This pigmentation extended through the whole thickness of the gut.

The process began sharply at the ileocecal valve and gradually faded out in the lower colon, so that in the rectum it was altogether absent. Analysis showed the pigment to be sulphide of bismuth. The bismuth was distributed chiefly in the lymph channels and lymph nodes. In dogs and cats there was also an ulcerative colitis, but the stomach and small intestines were normal.

In all three animal species a "parenchymatous nephritis" was found with necrosis of the epithelium and exudate into the glomerular capsules. The authors concluded (1) that the bismuth is absorbed very sparingly from the gastro-intestinal tract, but much more easier from the subcutaneous tissues; (2) that it is excreted from the kidney, from the mucosa of the mouth and of the large intestine where H_2S precipitates it, blocks the lymph channels, and

[1] Orfila (cited by Meyer and Steinfeld, Archives f. Experiment. Path., 1886, vol. xx, p. 40).
[2] Loc. cit.

thus produces stasis, necrosis, and ulceration. In the stomach and small intestine, owing to the absence of H_2S, the bismuth is not precipitated and no ulceration occurs. But in the mouth again we find H_2S, and so precipitation stasis and ulceration

Dalché and Villejean (*Arch. Gén. de Méd.*, August 1887, p. 129) produced in animals by the subcutaneous administration of bismuth or by dressing wounds with it, stomatitis, enteritis, and nephritis, and showed that the lesions were all connected with the channels of elimination through which the drug left the body. The bismuth is absorbed because the presence of albuminoids in the tissue renders it soluble. The absorption is slow but continuous and thus produces poisoning. All the buccal lesions of human cases were reproduced. Bismuth was precipitated from the urine and turned it black. Albumin and casts were present. Ulcerations of the intestine were produced.

The distribution of the metal in the organs was found to be as follows:

Spleen,	9 milligrams in 15 grams of tissue; total amount in the organ	17 mg.
Kidneys,	6 milligrams in 15 grams of tissue; total amount in the organ	45 mg.
Salivary glands,	5 milligrams in 15 grams of tissue; total amount in the organ	5 mg.
Liver,	2 milligrams in 15 grams of tissue; total amount in the organ	54 mg.

The liver therefore excretes the largest portion, though the concentration of the metal there is less than in the other organs mentioned.

By mouth absorption was slight when given in the ordinary salts and its comparatively short stay in the gastro-intestinal tract (as compared with long sojourn in abscess cavities and wounds) helps to account for its usual harmlessness.

The toxicity of bismuth (molecular weight 210) is in harmony with the toxicity of other heavy metals (lead and mercury). The lesions produced by the three metals in animals differ merely in intensity and are essentially identical. Intense lead poisoning spreads its discoloration over the oral mucosa and is not confined to the gum margin. On the other hand, mild bismuth poisoning may show only the "blue line" so familiar in ordinary (mild) plumbism. Paralyses, apparently of the peripheral type (as in plumbism), were produced in dogs by Dalché by the injection of bismuth.

SUMMARY AND CONCLUSIONS

1. Bismuth salts, used in the dressing of wounds and in the form of Beck's bismuth paste, may be absorbed and may produce poisoning notably similar to plumbism and mercurialism.

2. The metal is excreted chiefly by the kidney, in the mouth and in the large intestine. In these places it may produce lesions through the irritation of its presence.

3. Like lead it is precipitated wherever H_2S has access to it, as in the lymph channels of the mouth and large intestine.

4. It may produce a stomatitis, a black dotted line, and a colic similar to that of plumbism. The nervous system is much more rarely attacked than in plumbism and the blood shows no demonstrable changes.

5. When given by mouth it is rarely toxic, but in the 33 cases of poisoning here collected there were two in which the drug was given solely by mouth.

THE CLINICAL ANALYSIS OF SOME DISTURBANCES OF THE AUTONOMIC NERVOUS SYSTEM, WITH COMMENTS UPON THE SO-CALLED VAGO-TONIC AND SYMPATHETICOTONIC STATES

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Clinical men have long been dissatisfied with such terms as "nervousness," "neurasthenia," and "functional nervous disorders." The precise methods of analysis possible in certain well-understood organic diseases of the brain and spinal cord have, hitherto, been lacking in these so-called "functional nervous states," despite the excellent empirical descriptions of the phenomena observable.

Physicians have had, temporarily, to be content with recording a large number of more or less vague symptoms, occurring sometimes singly, more often, however, in groups. Many of these symptoms were obviously referable to abnormal states of functioning in the bloodvessels and in the internal organs (viscera), but no one saw his way clear to making actual anatomical diagnoses in such cases nor to the recognition of a "common band" running through them. The terms "cardiac neurosis," "nervous indigestion," "nervous diarrhea," vagal neurosis," "nervous asthma," "neurasthenia," "psychoneurotic disturbance," etc., indicate our clinical inclination to look upon such states as abnormalities of the nervous system, but clear conceptions as to the relations of these states to the normal neurophysiology of the viscera, or as to the character of the disturbance of the normal mechanisms responsible for the varying symptomatology, were conspicuously absent.

Of late years the frequency of such nervous disturbances (in visceral domains) in connection with disorders of the glands of internal secretion has also impressed many practitioners, especially those who see, and are interested in large numbers of "neurotic patients." In Graves' disease, particularly, such nervous manifestations are prominent, and make up no small proportion of the clinical syndrome; and in Addison's disease, in hypophysial diseases, and in diseases of the pancreas, the thyroid gland, the parathyroid glands, and the sexual glands, "nervous" manifestations are very common accompaniments. It is no wonder, therefore, that the interest of clinicians should recently have been aroused in attempts to interpret the inter-relations which exist here, and that a strong desire to replace the vague ideas up to now prevailing in this field with precise pathological, physiological, and etiological conceptions should have become evident. Members of this association have made laudable attempts in the direction mentioned. We recall especially Dr. Meltzer's painstaking studies of "inhibition" and Dr. Solis Cohen's articles on "vasomotor ataxia."

Progress in the analysis of pathological states is, of course, limited largely by the position of anatomical, and especially of physiological, knowledge; it is the privilege and the duty of clinicians, however, to see to it that pathological physiology is no laggard. For this reason it is essential that clinical men interested in visceral disturbances should, from time to time, take stock of the physiological and anatomical facts, and start again their clinical investigations from new points of vantage.

THE AUTONOMIC NERVOUS SYSTEM

Through the researches of recent years (Gaskell, Langley, and others) much new light has been thrown upon the structure and functions of the sympathetic nervous system, and this system has been found to be less independent of the rest of the general nervous system than previous investigators had thought.[1] We now know

[1] Langley, Jour. Physiol., Lond., 1898, xxiii, 240; also article in Schaefer's Text-book of Physiology, 1900, ii, 516; and the article in Asher-Spiro's Ergebnisse der Physiologie, 1903, ii, 808.

that the sympathetic system consists of neuronal conduction paths connecting the brain and spinal cord with certain parts of the body. The system contains both afferent and efferent paths, but anatomical studies indicate that the latter greatly predominate. These efferent paths of the sympathetic system differ from the efferent paths of the cerebrospinal nerves in several ways. In the first place, they innervate chiefly smooth muscle and secreting glands, while the efferent cerebrospinal nerves innervate only muscle and, indeed, only striped (voluntary) muscle. Again, while the efferent path of the cerebrospinal nerves consists of cell bodies and dendrites situated in the brain stem or the spinal cord and axones which traverse the whole distance from the gray matter to the muscles innervated without interruption (single nerve cells or neurones, the so-called "lower motor neurones"), the efferent path of the sympathetic system consists of at least *two neurones* instead of one. These two efferent neurones of the sympathetic efferent path are so arranged that the *proximal* one, the cell body of which lies in the gray matter of the spinal cord, has an axone which passes through the anterior root of a spinal nerve and through a white ramus communicans to the sympathetic trunks and then passes for a longer or shorter distance to terminate in an end-arborization (synapse) in some sympathetic ganglion (ganglion of sympathetic trunk; prevertebral ganglia; visceral ganglia) on the way to the smooth muscle or secretory gland which is to be innervated; in this ganglion, in which the axone of the proximal neurone ends, are situated the cell bodies of the *distal* neurones of the efferent sympathetic path; their axones extend from the ganglion to the smooth muscle (or the secretory gland) which is subject to the control of this particular conduction path. Since the axone of the proximal neurone extends from the spinal cord to a sympathetic ganglion, it has been called the *preganglionic fiber* of the conduction path; it is a medullated fiber. The axone of the distal neurone extends from the sympathetic ganglion to the end-organ, and hence is known as the *postganglionic fiber* of the path; it is, as a rule, a non-medullated fiber.

During recent years, thanks largely to the researches of the English physiologist Langley, it has been shown that certain other

efferent paths, not belonging to the sympathetic nervous system proper, are made up also of two neurones, one proximal and one distal, related to one another by a synapse in ganglia situated somewhere between the central nervous system and the periphery. These paths, too, convey efferent impulses to the same kinds of organs and tissues (indeed apparently to the very same organs and tissues) as do those of the sympathetic paths. The whole group of efferent paths, therefore, having the construction described, innervating chiefly smooth muscle and secreting glands, and including both the sympathetic paths and the other non-sympathetic paths, have been, according to Langley's suggestion, embraced under one name, the *autonomic* nervous system. It will be noted that this autonomic or "vegetative" system includes all the efferent nerve paths (outside the cerebrospinal axis) of the entire body, excepting only those innervating the voluntary muscles ("animal" system). We adhere, with Sherrington,[1] to this use of the term "autonomic," suggested by Langley, rather than to that of several European writers who exclude from it the sympathetic proper. Convenient as it would be to have a suitable term for the non-sympathetic component of the system, for use when contrasting it with the sympathetic proper, the priority of usage of the word autonomic in Langley's sense should, we think, be respected. With care, perhaps, the word autonomic can be used in both senses without confusion.

The *sympathetic proper* is really the portion of the autonomic system directly connected with the thoracic and lumbar portions of the spinal cord, its preganglionic fibers, in man, passing out through the anterior roots from the second thoracic to the second lumbar segment inclusive. It might be called, therefore, the *thoracolumbar autonomic system*. It sends its fibers to a great many different organs. Thus by way of the *superior cervical ganglion* it supplies (1) the dilator muscle of the iris, (2) the smooth muscle of the bloodvessels of the ear (including those of the eyeball and of the oral and nasal cavities), and (3) the salivary glands. By way of the *stellate ganglion* it innervates (1) the muscle of the

[1] "Sympathetic System" in the Encyclopedia Britannica, 1911, 11th edition, xxvi, 287.

heart (Nn. acceleratores) and (2) the smooth muscle and glands of the bronchi. By way of the *celiac ganglion* it innervates the smooth muscle and the glands of the stomach, intestine, biliary and pancreatic ducts, liver, pancreas, and kidney, as well as the bloodvessels supplying them. By way of the *superior and inferior mesenteric ganglia* it innervates the lower colon, sigmoid, and rectum, the urinary bladder, and the genital organs.

The non-sympathetic part of the autonomic system which may perhaps be called the *autonomic proper*, or *autonomic in the narrower sense,* including all remaining parts, is divisible into three portions; two of these are of *cranial* origin, viz.: (1) The *mid-brain* or *mesencephalic autonomic system,* and (2) the *hind-brain* or *rhombencephalic autonomic system;* one of them is of *spinal* origin, viz.: (3) The *sacral autonomic system.* The whole non-sympathetic part of the autonomic system may, therefore, also be designated as the *cranial-sacral autonomic system.*

The *mid-brain* autonomic system has preganglionic fibers which run in the N. oculomotorius to the ciliary ganglion; in the latter are the cell bodies which give off the postganglionic fibers of the system to innervate the muscle of accommodation (M. ciliare), and the muscle which contracts the pupil (M. sphincter iridis).

The *hind-brain* autonomic system sends preganglionic fibers into the N. facialis, the N. glossopharyngeus, and the N. vagus; the postganglionic fibers innervate the bloodvessels of the mucous membranes of the mouth, throat, nose, and paranasal sinuses, the salivary glands, the heart muscle (N. vagus), the glands, and musculature of the trachea and bronchi, the glands and musculature of the digestive tube from the esophagus to the colon (gullet, stomach, intestine, liver, and biliary passages, pancreas, and ducts), as well as the bloodvessels and tubules of the kidney.[1]

The *sacral* autonomic system, originating in the lower part of the spinal cord, sends its preganglionic fibers through the first three sacral nerves, all of them together being sometimes designated the N. pelvicus. The ganglia associated with the sacral

[1] On account of the great predominance of the N. vagus some writers speak of the whole autonomic system proper (exclusive of the sympathetic) as the "vagus system in the larger sense," hence the term "vagotony."

autonomic system are smaller cell groups, scattered among the pelvic organs which they innervate, the postganglionic fibers being distributed to the musculature and glands of the lower colon, sigmoid, rectum, anus, urinary bladder, and genital organs, and to the arteries of the rectum, anus, and internal and external genitals.

Here, then, we have two separate and distinct autonomic systems innervating the smooth muscle and the secreting glands of the entire body: (1) The sympathetic system proper (thoracolumbar autonomic), and (2) the autonomic system proper (mid-brain, hind-brain, and sacral autonomic), or "vagus system in the larger sense." Still a third system, the "enteric system" of Langley (plexuses of Auerbach and Meissner), influences the movements of the stomach and intestine; this third system possesses a certain independence, pendular and peristaltic movements continuing after section of all other nerves, but it is subject also to the two principal systems.[1]

PHARMACOLOGY OF THE AUTONOMIC NERVOUS SYSTEM[2]

We have called attention above to the fact that the whole efferent autonomic system—sympathetic as well as non-sympathetic, motor or inhibiting as well as secretory—is built up in the same way; now the whole system, it seems, behaves in a constant manner when nicotine is applied to the ganglion in which lies the synapse connecting the terminal of a preganglionic fiber with the cell body of the neurone which gives rise to a postganglionic fiber. *After a brief preliminary stimulation, nicotine interrupts the conduction path at the synapse.* Admitting slight variations in vulnerability in different animals, and in the different ganglia of the same animal, this law appears to be universally valid.

[1] The sweat glands, according to anatomical studies, are innervated by the sympathetic. In man they respond to drugs as though they were innervated by the non-sympathetic autonomic. It seems to us probable that the proof will eventually be brought that they, like other similar structures, are innervated by both systems. The pilomotor nerves are believed to belong to the sympathetic, also, but a double innervation is, we believe, not excluded.

[2] For an excellent presentation of the pharmacological reactions of the autonomic system, the reader is referred to Meyer and Gottlieb's Experimentelle Pharmakologie, II Aufl., Berlin u. Wien, 1911, p. 126.

Acting alike as regards nicotine, the two great subdivisions of the autonomic system nevertheless behave very differently (1) as regards their response to certain drugs and (2) as regards their physiological functions. Indeed, it would appear that the "sympathetic proper" is the physiological antagonist of the "autonomic proper."

If, as now seems certain, the organs are doubly innervated by antagonistic systems, the stimulation of one system producing an effect opposite to that following stimulation of the other system, it becomes exceedingly interesting to study (1) the influences which favor or inhibit the activity of each system in the normal body, and (2) the means at our disposal for artificially stimulating or inhibiting each system, especially through the action of drugs. The antagonistic physiological action of the two systems is well illustrated in the pupillary muscles—the dilator of the pupil is innervated by the sympathetic, the contractor of the pupil by the mid-brain autonomic. Another striking antagonism is obvious in the innervation of the heart—the sympathetic accelerates, while the hind-brain autonomic (N. vagus) slows the heart. To give a third example, stimulation of the sympathetic (superior cervical ganglion) inhibits salivary secretion and causes "dry mouth," while stimulation of the hind-brain autonomic (chorda tympani) causes "salivation." Almost everywhere, when the two innervations exist, the organs are antagonistically influenced by them.

Corresponding to this antagonism in physiological function, is the remarkably constant behavior of the two systems toward certain pharmacological agents. Thus epinephrin (or adrenalin), the principal active constituent of the suprarenal glands, when injected into the blood, or subcutaneous tissues, has the property of exciting all over the body precisely those physiological manifestations which follow upon stimulation of the efferent paths of the sympathetic system proper, and no others. Thus, electrical stimulation of the sympathetic causes vasoconstriction, accelerated heart action, dilatation of the pupil and viscid salivary secretion—so does epinephrin. Again, electrical stimulation of the sympathetic inhibits motility and secretion in the stomach and intestine—so

does epinephrin. Thus the whole sympathetic system proper behaves as a more or less homogeneous entity toward epinephrin; it is as though this substance had an elective affinity for the sympathetic neurones, as though it were definitely sympathicotropic in nature.[1]

Now epinephrin does not act in this way upon the terminals of the cranial-sacral autonomic system. We know, however, drugs—indeed, groups of drugs—which act almost as electively toward the cranial autonomic system as does epinephrin toward the sympathetic. Such drugs may be said to be vagotropic. On the one hand, there is *pilocarpin,* which on injection produces effects like those which follow electrical excitation of these autonomic endings; and other drugs (muscarin, physostigmin, cholin, digitalis) have a more or less similar effect, though differing from pilocarpin in some important details. On the other hand, there is *atropin,* which appears to paralyze these endings; at any rate, it is capable, when injected, of preventing the effects which usually result from cranial-autonomic stimulation; and other drugs (hyoscin, scopalamin, homatropin, eumydrin, and euphthalmin) have a somewhat similar effect. In the following table, compiled by Eppinger and Hess, and based partly upon the work of Fröhlich and Löwi,[2] partly upon the statements in Biedl's volume on internal secretion,[3] the effects of epinephrin (adrenalin) and sympathetic stimulation are contrasted with those of pilocarpin, ergotoxin, and cranial-sacral autonomic stimulation.

No general paralyzer of the sympathetic (comparable with epinephrin as a general excitant) is known. According to Dale,[4] ergotoxin paralyzes those sympathetic fibers which exert an exciting effect, but does not paralyze the sympathetic fibers which exert an inhibiting effect. Thus, after large doses of ergotoxin, stimulation of the vasoconstrictor sympathetic fibers no longer led to vasoconstriction and stimuli applied to the accelerator nerve did

[1] Or it may be possible, as Sherrington says, "that when a nerve is stimulated some body at the nerve ending is set free, and this, by combining with another chemical substance induces activity in the end organ (gland or muscle). It may be that when a sympathetic nerve is excited adrenalin is set free and combines with some substance which induces activity."

[2] Fröhlich and Loewi, Archiv f. exper. Pathol. u. Pharmakol., vol. lix, p. 34.

[3] A. Biedl, Innere Sekretion, Wien, 1910.

[4] Jour. Physiol., 1906, xxxiv, 163.

not increase the frequency of the heart beat; the inhibiting effect of the N. splanchnicus on the intestinal motility and of the sympathetic nerves which inhibit the bladder remained uninjured by this drug.

In the domain of the autonomic system proper, as the table shows, the drugs, both exciting and paralyzing, are less general in their effect than is epinephrin (adrenalin) in its effect on the sympathetic proper. The vagotropic drugs have more affinity for some parts of the cranial-autonomic system than for others. Even atropin, which acts fairly generally, has its maximal effect on the midbrain autonomic and grows gradually less efficacious as a paralyzer of the parts of the system situated more caudal-ward; in the domain of the sacral autonomic (N. pelvicus) it has almost no effect at all. Pilocarpin has its maximal effect on the secretory autonomic fibers, while its action on the cardio-inhibitory fibers is minimal; muscarin, on the other hand, exerts a powerful cardio-inhibitory influence, even bringing the heart to a standstill by irritation of the vagus.

Since in these doubly innervated organs the excitation of one system will produce an effect similar to that following upon a paralysis of the other system, it will be evident that the same functional manifestation may be due to different causes. Well-known examples of this, frequently cited, are (1) dilatation of the pupil due either to (*a*) excitation of sympathetic endings in the iris by means of adrenalin or cocaine, or to (*b*) paralysis of the autonomic terminals of the oculomotor nerve by means of atropin; and (2) increased frequency of the heart beat due either to (*a*) stimulation of the N. accelerans by large doses of caffein or to (*b*) paralysis of the N. vagus by atropin. Toxic effects in autonomic domains may, obviously, be very complex.

There is another fact which goes far to increase the complexity, viz., the demonstration that each of the individual antagonistic systems is to a certain extent double; thus the sympathetic proper may, in itself, carry some fibers favorable, other fibers unfavorable to a given function, and the autonomic proper may likewise. This fact will, in what follows, for the sake of simplicity of presentation, be ignored.

Effect of sympathetic stimulation.	Effect of Atropin	Effect of Epinephrin.	Organ.	Effect of Pilocarpin.	Effect of Ergotoxin.	Effect of cranial-sacral autonomic stimulation.
.... ..	Paralyzes	.....	Sphincter } Iridis.	Stimulates	.....	Stimulates (N. III).
Stimulates (Th. I and II)	.....	Stimulates	Dilator }	.....	.....	.....
.....	Paralyzes	.....	M. ciliaris	Stimulates	.....	Stimulates (N. III).
Stimulates (Th. I III)	.....	Stimulates	M. orbitalis (Mueller's)	Paralyzes	Paralyzes	
.....	Paralyzes	(Stimulates ?)	Salivary glands	Stimulates	.....	Stimulates chorda tympani.
Constricts (Th. II IV)	.....	Constricts	Cerebral bloodvessels	.....	.....	Dilates (N. X).
.....	.....	Dilates	Oral bloodvessels	.....	.....	Constricts (N. IX).
Constricts (Th. II–IV)	Constricts (?)	Constricts	Cutaneous bloodvessels of head			
.....	Dilates	Dilates	Coronary bloodvessels	Constricts		
Constricts (Th. II–L. IV)	.....	Constricts	Intestinal bloodvessels	.....	Dilates	
Constricts (L. I–IV)	.....	Constricts	Genital bloodvessels	.....	.....	Dilates (N. pelvicus).
Stimulates (Th. II–L. IV)	Inhibits	Inhibits	Sweat glands	Stimulates		
Stimulates (Th. IV–VII)	.....	Stimulates	Mm. arrectores pilorum (face)	.....	Paralyzes	
Stimulates (Th. I–V)	Stimulates	Stimulates	Heart muscle	Inhibits	Inhibits	Inhibits (N. X).
Relaxes (Th. II–IV)	Relaxes	Relaxes	Esophagus	Excites	.....	Excites (N. X).
Paralyzes (Th. II–L. IV)	Paralyzes	Paralyzes	Cardia	Excites	.....	Excites (N. X).
Diminishes (Th. II–L. IV)	Diminishes	.....	Tonus of stomach	Increases	.....	Increases (N. X).
Paralyzes (Th. II–L. IV)	Paralyzes	Paralyzes	Peristalsis of stomach	Increases	.....	Increases (N. X).
Diminishes (?)	Diminishes	Diminishes (?)	Secretion of stomach	Increases	.....	Increases (N. X).
Inhibits (Th. II–L. IV)	Paralyzes	Paralyzes	Motility of intestine	Excites	.....	Excites (N. X).
Relaxes (L. I–IV)	Relaxes	Relaxes	Colon	Excites	.....	Excites (N. pelvicus).
Relaxes (L. I–IV)	Relaxes (?)	Relaxes	M. sphincter ani	Cramps	.....	Cramps (N. pelvicus).
Relaxes (Th. II–L. IV)	Relaxes	Relaxes	Gall-bladder	Contracts	.....	Contracts (N. vagus).
Inhibits (?)	Inhibits	Inhibits	Pancreas secretion	Excites	.....	Excites (N. X).
.....	Inhibits	Inhibits	Bronchial musculature	Excites	.....	Excites (N. X).
Contracts (L. I–IV)	.....	Contracts	M. sphincter vesicæ	.....	.....	Inhibits (N. pelvicus).
Relaxes (L. I IV)	.....	Relaxes	M. detrusor vesicæ	.....	.....	Contracts (N. pelvicus).
.....	.....	Contracts	Uterus (pregnancy)	Relaxes	.....	.....
.....	.....	Relaxes	Uterus (gravid)	Contracts	.....	.....
Contracts (L. I–IV)	.....	Contracts	M. retractor penis	.....	.....	Relaxes (N. pelvicus).
Increases (Piqûre of Cl. Bernard)	.....	Increases	Sugar tonus	Diminishes	.....	.....
Increases (Piqûre vermis)	.....	Increases	Heat tonus	.....	.....	.....
Contracts	.....	Contracts	Pigment cells	Dilates	.....	.....

BALANCE AND LACK OF BALANCE OF THE ANTAGONISTIC AUTONOMIC INNERVATIONS: VAGOTONUS AND SYMPATHICOTONUS

Both of these antagonistic nervous systems appear to be constantly acting; in other words, the smooth muscle and the secreting glands are continuously innervated by both systems, and a certain "tonus" exists in each system. The pupil, for example, in medium illumination, stands midway between contraction and dilatation, its size being the resultant of the contraction of the M. sphincter iridis (mid-brain autonomic innervation) on the one hand, and the contraction of the M. dilator iridis (sympathetic innervation) on the other. Thus, there is a sort of balance maintained between the tonus of the autonomic proper (sometimes called vagotonus) and the tonus of the sympathetic proper (sympathicotonus). Similarly, in the heart, there is a normal balance between the continuous hind-brain autonomic innervation (N. vagus) and the continuous sympathetic innervation (N. accelerans), resulting in a pulse rate of approximately 72 per minute. Indeed, throughout the entire smooth musculature and the entire secreting-gland area of the body, such continuous antagonistic, but balanced, innervations may be assumed to exist, due to the maintenance of a fairly constant tonus in each of the antagonistic neurone systems. How is this normal equilibrium of continuous innervation, this balance of tonus, maintained? And what is it that happens when there is a departure from the equilibrium position in one direction or the other, in the performance of the various physiological functions of the organs?

There is much evidence to indicate that the antagonistic systems are subject to a double control: (1) A control exerted through the cerebrospinal axis, and (2) a control dependent upon direct chemical action upon the autonomic neurones themselves—the so-called hormones—dissolved in the tissue juices and having their origin in the glands of internal secretion. It is likely that both the central nervous system and the hormones play a part in the maintenance of the tonus in each system, and that either the central nervous system or a hormone can be the cause of a sudden excess of innervation in one or other system, as a whole, or in one of its parts.

In almost all mammals there is a constant flow of epinephrin (adrenalin) out of the suprarenal glands (Ehrmann); there is, therefore, good reason to believe that this epinephrin plays a part in keeping up the fairly constant general sympathetic tonus throughout the body. We are not so well-informed regarding the substance (or substances) responsible for the maintenance of tonus in the autonomic proper. It seems likely that such a single substance—a general "autonomin" or "vagotonin"—exists in the body, but, if so, we are not yet sure what it is. It might be a substance something like pilocarpin or physostigmin, drugs which as we have seen stimulate the autonomic proper in a fairly general way, though less generally than epinephrin (adrenalin) in the opposite system. It has even been suggested that cholin is the normal (hypothetical) "autonomin" we are looking for, but there are objections to that view. It is entirely possible that the normal tonus in the autonomic system proper is maintained by the combined effect of several different hormones, rather than by a single chemical substance, for, as we have seen, the drugs known to act upon this system (pilocarpin, physostigmin, muscarin, etc.) do not act on the whole system equally, but show a predilection for certain parts of it. One hormone, the so-called hypophysin or pituitrin, derived from the infundibular part of the hypophysis cerebri, appears to exhibit an exquisitely selective preference for certain parts of the vegetative system, exciting as it does the musculature of the rabbit's uterus to maximal contraction, and making it more accessible to nerve impulses arriving in it.[1]

The function of the suprarenal glands and of other parts of the chromaffin system seems to be inhibited normally by the physiological activity of the pancreas, for after extirpation of the pancreas in animals there is said to be excessive activity of the chromaffin system with overproduction of epinephrin and greatly heightened general sympathetic tonus.[2] An enfeebled chromaffin system with lessened epinephrin production (*e. g.*, in Addison's disease) leads to lowering of the sympathetic tonus so that the innervations in

[1] V. Frankl-Hochwart and A. Fröhlich, Wien. klin. Woch., 1909, No. 27.
[2] Eppinger, Falta, and Rüdinger, Zeitschr. f. klin. Med., lxvi and lxvii.

the domain of the opposite system, the autonomic proper, get the upper hand.

In short, though our knowledge regarding the effects of the various internal secretions is, as yet, in an embryonic state, still, the form that it has already assumed indicates that we are, by developing it, likely to arrive at an even better understanding of the exact physiology of the nerves which control the organs with whose functions we have, in inner medicine, so constantly to deal.

The relations of the central cerebrospinal nervous system to the maintenance of tonus in the antagonistic autonomic systems has thus far been but little studied. In view of Grünwald's[1] studies of the action of picrotoxin, which appears to cause *central* (not peripheral) excitation of the whole autonomic system proper (mid-brain, hind-brain, sacral), and Jonescu's researches, which hint at the possibility of a general central stimulation of the sympathetic, investigations in this direction, also, may prove to be rewarding.

If what has been said be accepted, the conception that disturbances of reciprocal control of these two antagonistic subdivisions of the great autonomic system, resulting in increased or decreased excitability, or in too high or too low a tonus of the single antagonists, can be a cause of pathological disturbances, will not occasion surprise. This conception has been definitely formulated, and discussed at considerable length, in the publications of Eppinger and Hess,[2] and no matter whether one can, or cannot, be in accord with all the ideas developed in connection with the conception, it must be admitted that it brings together under a unitary viewpoint a large number of important clinical manifestations, hitherto disparate and not regarded as belonging together.

These authors emphasize the necessity of making a distinction between "tonus" and "excitability." To illustrate, they contrast the influence of physostigmin with that of muscarin on the heart. Thus the former drug increases only the excitability of the vagus;

[1] Arch. f. exper. Pathol. u. Pharmakol., 1909, lx.

[2] Zeitsch. f. klin. Med., Berlin, lxvi; ibid., lxvii; and Die Vagotonie, Eine klinische Studie, Samml. klin. Abhandl. über Pathol. u. Therap. der Stoffwechs. u. Ernähr'st'n (von Noorden), Berlin, 1910.

in the absence of other stimuli this may lead to no visible effect. Muscarin, on the other hand, acting primarily as an irritant, can bring the heart to a standstill without the aid of other stimuli.

The variations of tonus of the vagus, as far as the heart is concerned, have long been appreciated by experimental physiologists and pharmacologists; that the variations of tonus in other domains should have received less consideration has doubtless been due partly to the difficulty of judging as to the condition of other organs, partly to the circumstances under which experiments are usually made (narcosis, curare-intoxication). Clinicians also have for a long time been impressed with some of the more striking phenomena referable to tonus variations in the vagus; we need only cite the great variation in response of different persons to the so-called vagotropic drugs. One may be little susceptible to atropin, while another reacts violently (mydriasis, accommodation paralysis, dry mouth, tachycardia, and hallucinations) to a relatively small dose. Again, one person may sweat scarcely at all after a good dose of pilocarpin, while another may be drenched with sweat, be salivated, and show an abundant flow of tears and of nasal secretion. Habitual bradycardia is common enough to excite remark and to point to a high vagus tonus in some people, especially among the young.

Believing that excessive reaction to pilocarpin, on the one hand, or to epinephrin (adrenalin), on the other, points to a high tonus (or a high excitability) of the autonomic proper in one instance, and of the sympathetic proper in the second, Eppinger and Hess have made use of injections of these two substances for diagnostic purposes. They believe that in many patients, met with in the clinic, they have been able to make out a definite "vagotonic constitution," characterized by (1) a hypersensitiveness to pilocarpin; (2) various clinical signs of heightened tonus throughout the whole domain of the cranial-sacral autonomic system, and (3) a relative insusceptibility to sympathetic stimuli.

In our own studies of patients in the Johns Hopkins Hospital, presenting symptoms which directed our attention to the possibility of an excessive sympathetic tonus, on the one hand, or an excessive vagotonus, on the other, we have been guided by the foregoing con-

siderations, and we have been much impressed, and certainly often surprised, by the enrichment of the clinical histories which have resulted. Taking one vagotonic sign, or one sympatheticotonic sign, as a clue, it has been very interesting to find how many other signs, vagotonic or sympatheticotonic, respectively, could, on more exact analysis, be discovered in the single cases. We have, during the last few months, with the aid of the assistant resident physicians and of several of the fourth-year students, systematically analyzed some 21 cases, which, for one reason or another, promised a "yield" of autonomic disturbances. In addition, a large number of patients though not so systematically studied, have been more or less carefully considered from the viewpoint of autonomic function.

Among the symptoms which may call attention to a heightened tonus in the cranial-sacral autonomic system may be mentioned the following:

A. *Symptoms in the domain of the mid-brain autonomic:* (1) Miosis, (2) accommodation spasm, (3) widened lid-slits, (4) von Graefe's sign.

B. *Symptoms in the domain of the hind-brain autonomic:* (*a*) *In the head:* (1) salivation, (2) epiphora, (3) hot flushes with vasodilatation. (*b*) *In the cardiovascular system:* (1) bradycardia, (2) slowed conduction time, (3) pulsus irregularis respiratorius, (4) some forms of extrasystolic irregularity, (5) low blood pressure, (6) angina pectoris vasomotoria. (*c*) *In the respiratory system:* (1) bronchial asthma, (2) irregular types of respiration, (3) laryngeal crises. (*d*) *In the digestive tract:* (1) inactive gag-reflex, (2) gastric hyperacidity, (3) gastric hypermotility and "gastric crises," (4) increased gastric tonus, (5) cardiospasm and pylorospasm, (6) "nervous" diarrhea, (7) "spastic" constipation, (8) mucous colitis.

C. *Symptoms in the domain of the sacral autonomic:* (1) Spasm of anal sphincter, (2) spasm of M. detrusor of bladder with pollakiuria, (3) priapism.

D. *Certain other symptoms:* (1) Eosinophilia, (2) tendency to sweating and especially to cold, clammy hands and feet, (3) lessened susceptibility to adrenalin-glycosuria, (4) oversensitiveness to

pilocarpin, (5) certain forms of pigmentation, (6) reflex over-excitability of N. vagus (slowing of heart on nasal stimulation or on compressing the eyeballs).

A comparison of the signs associated with heightened tonus in the craniosacral autonomic system (vagotonic signs) with those associated with heightened tonus in the sympathetic system (sympatheticotonic signs) is made in the accompanying table, taken from the inaugural dissertation of the younger von Noorden (1911):

	Vagotonic.	Sympatheticotonic.
Protrusio bulborum	—	+
Wide palpebral fissures	+ (?)	—
Psuedo-von Graefe test	+ (?)	—
Dalrymple		
Infrequent incomplete winking	—	+ (?)
Moebius test	—	+ (?)
Lagophthalmos	+	—
Epiphora	+	—
Difficulty in everting lid		
Löwi's test	—	+
Blood pressure	Low	High
Vasomotor instability, dermatographia, blushing, etc.	+	—
Pulse rate:		
Bradycardia	+	—
Tachycardia	—	+
Slow, after pressure on eyeballs	+	—
After atropin	Increased rate	Increased rate
Pulsus irregularis respiratorius	+	—
Eosinophiles	Eosinophilia	Eosinophilia
Urinary output	Diminished	Increased
Irregular type of respiration	+	—
Gastric analysis	Superacidity	Subacidity
Stomach:		
Size	. . . .	Atonic
Position	. . . .	Ptosis
Motility	Increased (*x*-ray)	
Intestinal motility:		
History	Diarrhea or spastic constipation	Atonic constipation
Glucose tolerance	Increased	
After epinephrin	No glycosuria	Strong glycosuria
Levulose tolerance:		
After epinephrin	No glycosuria	Strong glycosuria
Steatorrhea after 200 grams of butter	+	—
General nutrition		
Skin, sweating or dry	Sweating	Dry
Mouth, moist or dry	Moist	Dry
Glandular enlargement	+	—
Enlarged thymus	+	—
Gag reflex	Inactive	Increased
Pilocarpin	Strong reaction	
Adrenalin	No adrenalin glycosuria	Adrenalin glycosuria
Atropin	Decreased symptoms.	

PERSONAL OBSERVATIONS

During the last year the 21 patients whom we have studied with special reference to their visceral-nerve functions included the following:

Case 1. Exophthalmic goitre.
Case 2. Exophthalmic goitre.
Case 3. Psychoneurosis; psychasthenia; hyperthyroidism.
Case 4. Hyperthyroidism.
Case 5. Hyperthyroidism; v. Recklinghausen's disease.
Case 6. Hyperthyroidism; gastric neurosis (hyperacidity).
Case 7. Hyperthyroidism; gastric neurosis (hyperacidity).
Case 8. Bronchial asthma.
Case 9. Pulmonary tuberculosis (?); acromegaly.
Case 10. Bronchial asthma.
Case 11. Psychoneurosis; hysteria; syphilis (Wassermann).
Case 12. Epilepsy (?); v. Recklinghausen's disease; strongyloidosis.
Case 13. Psychoneurosis; neurasthenia.
Case 14. Psychoneurosis; neurasthenia; hyperthyroidism.
Case 15. Lipomatosis; hypopituitarism.
Case 16. Psychoneurosis; psychasthenia.
Case 17. Psychoneurosis; hysteria.
Case 18. Psychoneurosis; neurasthenia; pulmonary tuberculosis (?)
Case 19. Acrocyanosis.
Case 20. Exophthalmic goitre.
Case 21. Psychoneurosis; psychasthenia; hyperthyroidism.

Space will not permit us to publish the full clinical histories here. We shall be content at this time to present an epitome of our findings first as to the pharmacodynamic reactions obtained, and second, as regards the symptoms referable to disturbance of function of the visceral nerves. We shall then see how far it has been possible to correlate the clinical findings with the pharmacodynamic results obtained. Finally, the matter of pure vagotonic, pure sympatheticotonic and mixed types will be touched upon.

PHARMACODYNAMIC REACTIONS

As a means of differentiation of individual sensibility or oversensibility in one or the other vegetative nervous system, Eppinger and Hess lay emphasis upon the pharmacodynamic reaction. "In most instances antagonism has been proved," they say, and they believe that "high tonus in one system excludes heightened excitability in the other."

In our series, as an autonomic stimulant, *pilocarpin* was given hypodermically in doses of 0.011 to 0.0032 gram (gr. $\frac{1}{6}$ to gr. $\frac{1}{20}$); and *atropin*, hypodermically, in doses of 0.00043 to 0.00065 gram (gr. $\frac{1}{150}$ to gr. $\frac{1}{100}$) as an autonomic paralyzer. The sympathetic stimulant employed was *epinephrin* (adrenalin), 0.0005 and 0.001 gram at a dose, hypodermically. As examples, the results obtained in Cases 1 and 14 may be cited. These two patients (1 and 14) reacted in an outspoken way to both pilocarpin and epinephrin. In other words, each of the antagonistic systems seemed to be oversensitive. The reactions to pilocarpin, with salivation, sweating, and nausea, were supported by strong atropin reactions, of dry mouth, palpitation, and tachycardia. Case 1 with stronger pilocarpin reaction, was less susceptible to the effect of atropin; Case 14 showed more marked manifestations after atropin, but was stimulated less by pilocarpin, a contrast which is not surprising.

	Pilocarpin.	Atropin.	Epinephrin.
Case 1 Exophthalmic goitre.	0.0032 gram (h.); salivation, sweating, nausea, cough, belching, gagging; vasodilatation of face vessels; no epiphora; pulse from 70 to 90; temperature from 98.6° to 99.8°; blood pressure from 110 to 95.	0.00043 gram (h); dry mouth and throat; pulse from 70 to 104.	0.0005 gram (h.); rigor; sense of cold; nausea; shivering and tremor; glycosuria; blood pressure from 105 to 135.
Case 14. Psychoneurosis, neurasthenia, hyperthyroidism.	0.011 gram (h.); marked salivation, sweating, nausea, headache, abdominal discomfort; no epiphora.	0.00108 gram (h.); palpitation; dry mouth and throat, oppression over heart; slight difficulty in breathing; pulse from 74 to 104.	0.001 gram (h.); palpitation; tremor; headache; glycosuria; blood pressure from 100 to 166.

But both patients were definitely epinephrin-sensitive, and reacted with tremor, headache, sense of cold, glycosuria, and increase of blood pressure.

Cases 18 and 12 may also be considered here, as they illustrate a similar reactive power in each of the two antagonistic systems. Patient 18 exhibited salivation, sweating, vasodilatation, and dermatographia after pilocarpin; palpitation and shortness of breath after atropin; but also slight glycosuria and increase of blood pressure after epinephrin—a rather mild reaction to each of the three drugs. Patient 12, on the other hand, yielded no recognizable reaction to either pilocarpin or epinephrin.

	Pilocarpin.	Atropin.	Epinephrin.
Case 18. Psychoneurosis, neurasthenia, pulmonary tuberculosis (?)	0.0054 gram (h.); salivation; sweating; vasodilatation; dermatographia; blood pressure from 135 to 115.	0.00065 gram (h.); palpitation; no dryness of mouth; no change in pulse.	0.0005 gram (h.); palpitation; "beating in body;" "medicine too strong;" glycosuria; pulse from 68 to 96; blood pressure from 100 to 140.
Case 12. Epilepsy (?) strongyloidosis.	0.0032 gram (h.); no symptoms or signs of reaction.		0.001 gram (h.); no glycosuria.

We may now turn to a group of six cases, 3, 5, 8, 9, 10, and 11, which were definitely *pilocarpin-sensitive*. They exhibited, on pilocarpin injection, salivation, epiphora, sweating, flushing, and dermatographia, the reactions varying slightly in degree. All the patients but one (Case 8) reacted moderately to atropin. In no one of the six was glycosuria produced by epinephrin, nor were other manifestations referable to epinephrin-sensitiveness noticeable.

	Pilocarpin.	Atropin.
Case 3. Psychoneurosis, psychasthenia, hyperthyroidism.	0.011 gram (h.); salivation, sweating, flushed face and trunk, epiphora, dermatographia.	0.00054 gram (h.); dry mouth; no change in pulse.
Case 5. Hyperthyroidism.	0.0032 gram (h.); salivation, sweating, epiphora, vasodilatation, headache; temperature from 98.5° to 99.5°.	0.00054 gram (h.); dry mouth, deeper respirations, palpitation; pulse from 80 to 95; blood pressure from 130 to 115; temperature from 98° to 99.5°.
Case 8. Bronchial asthma.	0.0032 gram (h.); salivation, sweating, sense of warmth, vasodilatation.	0.00054 gram (h.); no reaction.
Case 9. Pulmonary tuberculosis (?) acromegaly.	0.003 gram (h.); epiphora, sweating; vasodilatation; giddiness; headache; nausea; muscle cramp; no salivation.	0.00054 gram (h.); dry mouth; dry skin; shallow respirations; no change in pulse.
Case 10. Bronchial asthma.	0.0032 gram (h.); salivation, sweating; vasodilatation about head; no epiphora.	0.00043 gram (h.); relief of asthmatic attacks; palpitation; sticking in throat.
Case 11. Psychoneurosis, hysteria, syphilis (Wassermann).	0.0032 gram (h.); slight salivation; epiphora, and sweating.	0.00054 gram (h.); slight dryness of mouth; pulse increased; blood pressure lowered.

Nine of the remaining 11 cases, not sensitive to pilocarpin, are classes as epinephrin-sensitive on the basis of one of the following three reactions:

1. General reaction, observable in the most sensitive cases (Cases 4, 15, and 19), reacting with increase in blood pressure, headache, nausea, tremors, and glycosuria. In Case 19 the reaction, "funny feeling," numbness, sense of constriction about the jaws, and increase in blood pressure, followed simple instillation in the conjunctival sac. In all 3, very slight symptoms of moist mouth or sense of warmth followed pilocarpin injection, and slight dryness of mouth or slight palpitation, after atropin injection.

	Pilocarpin.	Atropin.	Epinephrin.
Case 4. Hyperthyroidism.	0.0032 gram (h.); salivation slight; pulse from 100 to 84; blood pressure from 110 to 98.	. . . . .	0.001 gram (h.); headache; numb extremities; dry mouth, nausea; clonus of jaw muscles; glycosuria; blood pressure from 105 to 135.
Case 15. Lipomatosis, hypopituitarism.	0.0011 gram (h.); slight salivation; sense of warmth, and headache.	0.00081 gram (h.); slight palpitation and dry mouth; no change in pulse.	0.001 gram (h.); marked glycosuria; blood pressure from 100 to 125.
Case 19. Acrocyanosis.	0.0032 gram (h.); slight sense of warmth.	0.00054 gram (h.); slight dryness of mouth.	0.0005 gram; funny feeling and numbness over body after instillation in eye; sense of constriction of jaws; blood pressure from 118 to 128.

2. Outspoken glycosuria (Cases 7, 16, 20, and 21). The patients voided 11, 4.15, 7.6, and 3 grams of glucose respectively in the hours following the epinephrin injection; there was little or no change noticeable after pilocarpin or atropin injection.

3. Slight epinephrin glycosuria, and no reaction to pilocarpin or atropin (Cases 13 and 17).

In Case 6, slight glycosuria (0.264 gram) followed administration of epinephrin. Pilocarpin and atropin were not tried in this case.

In Case 2 no pharmacodynamic tests were made (a private case operated upon as an emergency).

CASES GROUPED ACCORDING TO THE CLINICAL SYMPTOMS PRESENTED

The clinical manifestations of increased tonus and excitability have been discussed above. Their occurrence on the craniosacral autonomic side in our series of cases will be seen in the following table:

An examination of this table shows the very variable incidence of symptoms in the separate domains of the craniosacral autonomic system. Thus, the cases fall into groups as follows:

A. *Mid-brain autonomic symptoms:*
   Marked, 5 cases (1, 2, 3, 9, and 20).
   Moderate, 5 cases (5, 11, 15, 19, and 21).
   None, 11 cases (4, 6, 7, 8, 10, 12, 13, 14, 16, 17, and 18).

B. *Hind-brain autonomic symptoms:*
   1. Cephalic—
      Marked, 2 cases (3 and 16).
      Moderate, 4 cases (1, 11, 20, and 21).
      Mild, 10 cases (2, 4, 6, 7, 10, 13, 15, 17, 18, and 19).
      None, 5 cases (5, 8, 9, 12, and 14).
   2. Cardiovascular—
      Bradycardia, 10 cases (1, 4, 6, 7, 8, 12, 13, 14, 16, 17).
      Other less important manifestations, 3 cases (2, 19, 21).
      None, 8 cases (3, 5, 9, 10, 11, 15, 18, and 20).
   3. Respiratory—
      Asthma, 3 cases (8, 9, and 10).
      Irregular respirations, 3 cases (1, 2, and 3).
      No manifestations, 15 cases (4, 5, 6, 7, and 11 to 21).
   4. Digestive—
      Hyperacidity with other manifestations, 5 cases (2, 4, 6, 7, and 14).
      Other less important manifestations, 12 cases (1, 3, 5, 8, 12, 13, 15, 16, 17, 18, 20, and 21).
      None, 4 cases (9, 10, 11, and 19).

C. *Sacral autonomic symptoms:*
   No manifestations observed in any of the cases.

D. *Miscellaneous autonomic symptoms:*
   1. Eosinophilia—
      5 to 19 per cent., 3 cases (10, 12, and 13).
      1 to 4 per cent., 7 cases (7, 9, 14, 15, 16, 19, and 21).
      0 to 1 per cent., 11 cases (1 to 6, 8, 11, 17, 18, and 20).
   2. Cutaneous—
      Marked sweating, dermatographia, cold, moist hands, and pigmentation, 14 cases (1, 2, 3, 4, 6, 7, 8, 14, 15, 16, 17, 18, 19, and 20).
      Less marked, 5 cases (9, 10, 12, 13, and 21).
      None, 2 cases (5 and 11).

CLINICAL MANIFESTATIONS OF VAGOTONUS

| | A. Midbrain Domain: | | | | | B. Hindbrain Domain: 1. Head. | | | | | | 2. Cardiovascular. | | | | | |

| | | |

3. Increased sugar (glucose) tolerance—
   Definite, 4 cases (8, 9, 12, and 15).
   Probable, 6 cases (10, 13, 16, 17, 19, and 21).
   Not increased, 10 cases (1, 3, 4, 5, 6, 7, 11, 14, 18, and 20).
   Increased levulose tolerance proved in Case 15.
4. Diminished urinary output—
   12 cases (1, 2, 3, 6, 7, 9, 11, 12, 17, 18, 19, and 21).
5. General glandular enlargement—
   Marked, 2 cases (14 and 17).
   Slight, 5 cases (7, 8, 9, 10, and 11).

The "sympatheticotonic" clinical signs observed are recorded in the following table:

CLINICAL MANIFESTATIONS OF SYMPATHETICOTONUS

Case.	Exophthalmos.	Möbius' sign.	Löwi phenomenon.	Increased blood pressure.	Tachycardia.	Gastric sub- or anacidity.	Polyuria.	Diminished glucose tolerance.	Epinephrin glycosuria.
1	+	+	+	0	0	+	0	+	Marked
2	+	+		+	+	0	0		
3	+	+		+	0	0	0	0	
4	0	+		0	0	0	0	0	Slight
5	+	0		+	0	0	+	0	None
6	0	0		+	0	0	0	0	None
7	0	0	0	+	0	0	0	0	Marked
8	0	0		0	0	+	+	0	None
9	0	+		+	0	0	0	0	
10	0	0		+	0	0	+	0	None
11	+	+		+	0	0	0	0	Slight
12	0	0		+	0	0	0	0	None
13	0	0		+	0	+	+	0	Slight
14	+	0		0	0	0	+	0	Slight
15	+	+		+	0	0	+	0	Slight
16	0	0		+	0	0	+	0	Moderate
17	0	0		+	0	0	0	0	Slight
18	0	0		+	0	+	0	0	Slight
19	+	+	+	+	0	0	0	0	None
20	+	+		+	0	+	+	0	Marked
21	+	0		+	0	0	0	0	Moderate

CORRELATION OF THE PHARMACODYNAMIC REACTIONS AND THE CLINICAL MANIFESTATIONS

Several questions naturally arise at this point. Do the pharmacodynamic reactions, as has been claimed, correspond to clinical types of increased tonus and excitability in one or the other system? Are the pharmacodynamic results in either the craniosacral autonomic or in the sympathetic system supported by the clinical manifestations observed? Again, is increased tonus and excitability in one system associated with a correspondingly diminished tonus in the antagonistic system, as shown by pharmacodynamic tests or in the clinical symptoms observable?

We may consider first a series of 6 cases which yielded definite reactions on pilocarpin injection, and also on atropin injection (Cases 3, 5, 8, 9, 10, and 11). They were not epinephrin-sensitive. Pharmacodynamically then they would be considered "vagotonic" cases. Let us see in how far their clinical symptoms were also vagotonic in type. The symptoms presented in these 6 cases were as follows:

VAGOTONIC MANIFESTATIONS IN PILOCARPIN-SENSITIVE CASES

Cases.	Hind brain.						Miscellaneous.				
	Midbrain.	Head.	Cardio-vascular.	Respiratory.	Digestive.	Sacral.	Eosino-philia.	Skin.	Glucose tolerance.	Urinary output.	Gland en-largement.
3	Marked	Marked	None	Moderate	Moderate	None	None	Marked	No incr.	Dim.	None
5	Moderate	None	None	None	Moderate	None	None	None	No incr.	No dim.	None
8	None	None	Marked	Marked	Moderate	None	None	Marked	Incr.	No dim.	Slight
9	Marked	None	None	Marked	None	None	Slight	Moderate	Incr.	Dim.	Slight
10	None	Mild	None	Marked	None	None	Definite	Moderate	Incr.	No dim.	Slight
11	Moderate	Moderate	None	None	None	None	None	None	No incr.	Dim.	Slight

It is apparent from this table that none of the 6 exhibits vagotonic signs in all domains. There is no sure way of prophesying in which craniosacral autonomic domain the symptoms will be most conspicuous. To a certain extent the ordinary clinical diagnosis may give a hint. Thus patients 8 and 10 suffered from bronchial asthma; and the respiratory symptoms of the hind-brain domain were the conspicuous symptoms. Mid-brain autonomic signs are marked in patients 3 and 9, both cases of hyperthyroidism. The manifestations are only slight in any of the domains in patient 5 (malaria with mild hyperthyroidism), and patient 11 (hysteria with syphilis). The pilocarpin-sensitive cases, then, have shown vagotonic clinical signs in one domain or another, but not evenly throughout all craniosacral autonomic domains.

We may next consider the epinephrin-sensitive individuals. Three patients (4, 15, and 19) yielded general reactions to epinephrin. Pharmacodynamically, they were therefore sympathetico-tonic. Their clinical manifestations on the sympathetico-tonic side are summarized in the following table:

Sympathetico-tonic Signs Met with in Epinephrin-sensitive Cases

Case.	Adrenalin glycosuria.	Löwi's test.	Eyes.	Blood pressure.	Pulse.	Stomach.	Kidneys.
4	Marked	?	Marked	Low	Slow	None	Normal
15	+ amount ?	?	Marked	Normal	Normal	None	Polyuria
19	None	Positive	Marked	Normal	Normal	None	Dim.

The table shows how variable the clinical manifestations of increased sympathetic tonus and excitability may be in cases reacting markedly to the corresponding pharmacological test. The 3 patients agree in exhibiting exophthalmos and poor convergence of the eyes; they disagree strikingly as regards other sympathetico-tonic signs.

In the 4 cases (7, 16, 20, and 21) of outspoken glycosuria following epinephrin injection, the sympathetico-tonic manifestations were as follows:

Case.	Epinephrin glycosuria.	Löwi's test.	Eyes.	Blood pressure.	Tachy-cardia.	Stomach.	Polyuria.
7	Marked	Negative	None	Normal	None	None	None
16	Moderate	?	None	High	None	None	Positive
20	Marked	?	Marked	Normal	None	Marked	Positive
21	Moderate	?	Moderate	High	None	None	None

These patients show the same variability as to general sympatheticotonic signs. In fact, the extreme variation in degree (the total absence in case 7, and the most marked presence in case 20) occurs in the 2 cases with the most marked epinephrin glycosuria.

Slight epinephrin glycosuria occurred in 3 cases (6, 13, and 17). They yielded clinically practically no other sympatheticotonic signs.

Case.	Löwi's test.	Eyes.	Blood pressure.	Tachycardia.	Stomach.	Polyuria.
6	?	None	High	None	None	None
13	?	None	Normal	None	Moderate	Present
17	?	None	Normal	None	None	None

Slight epinephrin glycosuria (less than 1 per cent.) is not, therefore, a reliable index of a general clinical sympatheticotonic state. Only 1 of these 3 cases showed any clinical sympatheticotonic signs, and they were very mild.

It has been stated that 2 cases (1 and 14) reacted markedly to drugs which stimulate both the vagus and the sympathetic. A corresponding condition was found clinically. Case 1 showed well-marked manifestations in both vagal and sympathetic systems; case 14, contrasting in degree, exhibits equally mild signs in both systems.

Case	Mid-brain.	*Cranio-sacral Autonomic.* Hind brain.				Sacral	Miscellaneous.					*Sympathetic.*						
		Head.	Cardio-vascular.	Respir-atory.	Diges-tive.		Eosino-philia.	Skin.	Glucose tolerance.	Urinary output.	Gland enlarge-ment.	Epinephrin glycosuria.	Löwi's test.	Eyes.	Blood pres-sure.	Pulse.	Stomach	Polyuria.
Case 1	Marked	Moderate	Marked	Mild	Mild	None	None	Marked	No incr.	Dim.	None	Marked	Positive	Marked	Normal	Slow	Moderate	Absent
Case 14	None	None	Mild	None	Moderate	None	Present slight	Marked	No incr.	Normal	Present	Present amount?	?	Moderate	Normal	Slow	None	None
Case 18	None	Mild	None	None	Mild	None	None	Moderate	No incr.	Dim.	None	Present amount?	?	None	Normal	Normal	Moderate	None
Case 12	None	None	Mild	None	None	None	Present	Moderate	Incr.	Dim.	None	None	?	None	High	Slow	None	None

Case 18, with relatively mild response to both pilocarpin and epinephrin, shows equally mild signs of both vagotonic and sympatheticotonic states.

Case 12 gave no reaction to either drug, and shows practically no manifestations in either nervous system.

The question of correlation of pharmacodynamic reactions and clinical manifestations may now be approached from another direction. In how far are the clinical instances of markedly increased tonus and excitability associated with outspoken pharmacodynamic reactions of the same system? Here we shall consider the cases by special domains and shall cite only the *marked* clinical cases.

VAGOTONIC SIGNS CONSPICUOUS

	Case.	Pilocarpin reaction.	Atropin reaction.
Mid-brain domain	1	Marked	Moderate
	3	Marked	Slight
	9	Marked	Marked
	20	Slight	Slight
Hind-brain domain (head)	3	Marked	Slight
	16	?	None
Cardiovascular (bradycardia)	1	Marked	Moderate
	4	Slight	?
	6	?	?
	7	?	None
	8	Marked	None
	12	None	?
	13	None	None
	14	Marked	Marked
	16	?	None
	17	None	None
Respiratory (asthma)	8	Marked	None
	9	Marked	Marked
	10	Marked	Marked
Digestive (hyperacidity	2	?	?
	4	Slight	?
	6	?	?
	7	?	None
	14	Marked	Marked
Eosinophilia	10	Marked	Marked
	12	None	?
	13	None	None
Increased sugar tolerance	8	Marked	None
	9	Marked	Marked
	12	None	?
	15	Slight	Slight

This table shows that of 28 instances of marked clinical "vagotonic" manifestations in some domain, there were 18 instances of positive reaction to vagotropic drugs.

Sympatheticotonic Signs Conspicuous

	Case.	Epinephrin reaction.
Löwi test	1	Marked
	19	Marked
Exophthalmos (Möbius' sign)	1	Marked
	3	?
	4	Marked
	5	None
	9	None
	11	None
	14	Marked
	15	Marked
	19	Marked
	20	Marked
	21	Marked
High blood pressure	3	?
	5	None
	9	None
	10	None
	11	None
	12	None
	16	Marked
	21	Marked
Subacidity	1	Marked
	8	None
	13	Slight
	18	Slight
	20	Marked
Polyuria	5	None
	8	None
	13	Slight
	14	Marked
	15	Marked
	16	Marked
	20	Marked

Here, in 31 instances of marked clinical sympatheticotonic manifestations of one or another sort, there were 20 instances of positive reaction on epinephrin injection.

Estimated from the above study, it would seem that a conspicuous vagotonic or sympatheticotonic sign may also be a mark of a pilocarpin- or epinephrin-sensitive individual in about 64 per cent. of the instances.

Finally, a word as to the evidence in favor of the views that an exaggeration tonus (or of excitability) in one of the reciprocally antagonistic systems is accompanied by a diminution of tonus (or of excitability) in the other. It is difficult to estimate the degree of excitability and tonus from the clinical manifestations alone as an examination of the preceding tables suggests. In the following table an attempt has been made to discriminate, as accurately as

possible, by means of the terms "marked," "moderate," "mild," or "none," among both the pharmacodynamic reactions and the clinical manifestations.

	Pilocarpin reaction.	Epinephrin reaction.	Pharmaco-dynamic relation.	Clinical vagotonus.	Clinical sympa-theticotonus.	Relation.
Case 1 . . .	Marked	Marked	V = S	Marked	Marked	V = S
Case 14 . . .	Marked	Marked	V = S	Moderate	Moderate	V = S
Case 18 . . .	Moderate	Moderate	V = S	Mild	Mild	V = S
Case 12 . . .	None	None	V = S	Mild	Milder	V > S
Case 3 . . .	Marked	None	V > S	Moderate	Mild	V > S
Case 5 . . .	Marked	None	V > S	Mild	Mild	V = S
Case 8 . . .	Marked	None	V > S	Moderate	Mild	V > S
Case 9 . . .	Marked	None	V > S	Moderate	Mild	V > S
Case 10 . . .	Marked	None	V > S	Marked	Mild	V > S
Case 11 . . .	Moderate	None	V > S	Mild	Mild	V = S
Case 4 . . .	Slight	Marked	V < S	Moderate	Mild	V > S
Case 15 . . .	Slight	Marked	V < S	Moderate	Moderate	V = S
Case 19 . . .	Slight	Marked	V < S	Moderate	Mild	V > S
Case 7 . . .	None	Marked	V < S	Moderate	Mild	V > S
Case 16 . . .	None	Marked	V < S	Moderate	Mild	V > S
Case 20 . . .	Slight	Marked	V < S	Moderate	Moderate	V = S
Case 21 . . .	Slight	Marked	V < S	Moderate	Mild	V > S
Case 13 . . .	None	Slight	V < S	Moderate	Moderate	V = S
Case 17 . . .	None	Slight	V < S	Marked	Mild	V > S
Case 6 . . .	?	Slight	V : S (?)	Moderate	Mild	V > S
Case 2 . . .	?	?	V : S (??)	Marked	Marked	V = S

These tables show a harmonious agreement between pharmacodynamic reactions and clinical manifestations in only 7 of 19 cases. In 2 with increased pilocarpin-sensitiveness the clinical vagotonic and sympatheticotonic signs were approximately equal. The same is true of 3 epinephrin-sensitive individuals; whereas, clinically, vagotonic signs predominated in 5 epinephrin-sensitive cases.

DISCUSSION

Dr. S. Solis Cohen: I have been much interested in this admirable exposition, confirming, as it does, my twenty-five-year-old observations; especially upon the point that diagnosis in these cases must be of the individual and not alone of the particular symptom-group that he may happen to present at a special time. In more recent papers I have recognized that the title *ataxia autonomica* would be more comprehensive than my original suggestion of *vasomotor ataxia*. But I hold to, and must again emphasize, the fact that these phenomena are most largely ataxic—incoördinate—manifestations. In my first paper I divided them according to the vascular tonicity, into constrictive, dilative (or spastic and ectatic)

and mixed. The mixed group is clinically the largest. Graves' syndrome is a marked type of dilative—what is termed in the paper vagotonic—disorder, although its cardiac phenomena are by no means vagotonic. Raynaud's disease, when pure, is an example of the extreme constrictive—or what the paper terms sympathico-tonic—type. But just as in Graves' syndrome there are some constrictive phenomena, so even in Raynaud's syndrome there may be dilative symptoms. Indeed, as I have shown by cases published—a fraction only of records on file—the phenomena of Graves and Raynaud are sometimes commingled in one individual. Hence, while an individual may be predominantly sympathico-tonic or vago-tonic—to use the terms of the paper—but without accepting them—yet these divisions are neither constantly sharp in the clinical picture of his varying and manifold disorders, nor sufficiently fundamental in theory. Back of the abnormal tone is the lack of taxis in the common centres—and I include peripheral subcentres in this designation—while beyond the central disorder is an unknown anatomical or chemical abnormity, nearly always congenital and usually inherited. Moreover, there are complex questions of local determination and of organized association of symptoms to consider, which time would not now permit me to discuss, even were knowledge sufficient, as it is not. Whether the functions and interrelations of the autonomic system and the sympathetic system—using again the terms of the paper, but not admitting their propriety—are so clean cut as the diagram would indicate is open to question, despite the great authority of the investigators upon whose work it is based. Both psychology and physiology are investigating the problem, but neither has yet solved it. The suggestion has been made that one set of ganglia and fibers responds to external stimuli, the other to internal stimuli; but that, too, is far from proved. Nor is it at all clear that we can predicate a constant sharp opposition of the "blue" and the "red;" for carry back some of the red lines to the ultimate origin of their stimuli—preganglionic, of course—and you will come up into the "blue" bulbar region. Moreover, it is perfectly clear clinically that paresis as well as overstimulus is to be considered. These studies are valuable; they carry the question on; but they do not answer it. As regards the inter-relation of the hormones or internal secretions, this also is not as yet clearly and fully demonstrated. I have elsewhere published my own views and need not repeat here. One ought, in discussing it, at least refer to the encyclopedic literary researches of Sajous. By criticism and analysis of experimental work and pathological studies, he has arrived at certain conclusions, some of which have since been put forth by others and accepted; while some are not in accord with general scientific opinion; but whatever his errors may be, his positive stimulating contributions to medical thought should be recognized.

Dr. L. B. Wilson: This address of Dr. Barker's has been particularly interesting to me in connection with some work by Gley, of the University

of Paris, published last December, showing the results of injection into the vascular system of dogs of extracts of human thyroids. We have been repeating Gley's work recently in the last three or four months, and I need only to say that we have been able to corroborate it. I am sure it will be interesting to members of the Association who are not familiar with Gley's work to know that he has been able not only to produce a fall in blood pressure by injection of thyroid extract, but also to inhibit the vagus. Gley was unable to do this when injecting normal fluid or when injecting colloid fluids. He succeeded in doing it in the injection of two exophthalmic goitres, and he thought he got doubtful result in injecting from another exophthalmic case. I have been able to confirm his observations with exophthalmic material, and in two well-defined cases of exophthalmic goitre where we used the serum of the patient. It is a most interesting phenomena. It is quite true that we can get a fall of blood pressure by injecting extracts of glands, as in injecting extracts of hypertrophied prostates. We have not, however, been able to inhibit the vagus with any extracts or serum from any case but exophthalmic goitre cases. Our experiences are limited; we have studied 15 to 20 cases and some 40 to 50 dogs. I may say that in some dogs which we have been experimenting upon after we succeeded in getting our fall of blood pressure and our inhibition of the vagus, we let the dog recover until the pressure was back to 150 to 180 mm., then the exhibition of adrenalin brought about the usual increase of pressure.

Dr. S. J. Meltzer: I wish to express my admiration for Dr. Barker who mastered these very intricate combinations, but I wish to say in the interest of sound progress in medicine that 95 per cent. of that is pure and simple hypothesis. Furthermore, some of the facts are far from being verified. Hypotheses are indispensable for work; but statements which consist of only 5 per cent. facts and 95 per cent. hypotheses may serve rather to impede the sound progress of knowledge.

Dr. L. F. Barker: Dr. Meltzer has emphasized the small amount of actual knowledge that we have, as yet, regarding the internal secretions and the autonomic system. It is very difficult, in the few minutes we have in the meeting here to do more than give a general impression of a subject; I trust that when the members of the Association read the full paper they will feel that the facts mentioned and the hypotheses are easily distinguishable from one another. Of course it would never do for us to care more for hypotheses than for facts. At the same time, we find out new facts by forming hypotheses. No man works without an hypothesis. So long as we use hypotheses only to stimulate work, to clarify our views, or to hold even temporarily widely separated facts together, I think they may be most helpful.

NITROBENZOL POISONING

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From time to time various countries have studied industrial poisons, but it is only recently that there has been revealed accurate information concerning the dangers to health and life from their use in the various manufactories. We were content to believe that our employees were not subjected to the dangers which prove so detrimental to industrial workers in foreign countries, but the *Bulletin of the Bureau of Labor*[1] upon this subject, with its list of such poisons, has disclosed the fact that not only were our factory hands as susceptible to the industrial poisons as the workers in foreign factories, but also that it only required systematic investigation to show that a large number of cases of disease and death among wage-earners was due to exposure to such poisons while employed in the factories.

About fifteen years ago an attempt was made to study the poisonous effects of nitrobenzol upon employees of factories in which this chemical was used. A letter was sent to several large well-known firms asking the effect of nitrobenzol on the employees, the number of cases of poisoning, the symptoms, the treatment, and the result. Very few replied, and of them one denied its use, one had no information to give, and a third admitted its use and its deleterious effects on its employees, but declined to give data. The investigation was then abandoned.

Sometime ago Mr. H. O. Hall, of the Library of the Surgeon General's Office, United States Army, made a study (not published) of the poisonous effects of nitrobenzol in a "Fatal Case of Poisoning from Shoe-blacking."

[1] No. 100, May, 1912.

Kober,[1] in his article on "Industrial Hygiene," mentions nitrobenzol as one of the industrial poisons, "which is used in making aniline and in the manufacture of roburite and other explosives."

Witthaus,[2] describes pure nitrobenzene $C_6H_5NO_2$ as a pale yellow, oily liquid, sp. gr. 1.186, b. p. 205° (401° F.), insoluble in water, very soluble in alcohol, and of purely chemical interest. The commercial product is manufactured as an intermediate in obtaining aniline from benzene. It is also known as oil or essence of mirbane, a mixture of nitrobenzene and nitrotoluene, $C_6H_4CH_3NO_2$, in varying proportions according to the use for which it is destined. It is a yellow or brownish oil, having a pronounced odor of peach kernels, and a sweetish taste. It is used in the aniline industry, in the manufacture of explosives and of shoe-blacking, and in the preparation of soaps, perfumes, confectionery, liqueurs, and flavoring extracts, under the misleading name of "artificial oil of bitter almonds." Its chemical relationship to the true oil of bitter almonds, which, when purified, consists essentially of benzoic aldehyde, C_6H_5CHO, is not close.

The Bureau of Labor defines nitrobenzol (mirbane oil, imitation bitter almond oil), $C_6H_5NO_2$, as a colorless, highly refractive fluid, having an odor like that of bitter almonds, and all nitrocompounds of benzol and its homologues, *e. g.*, denitrobenzol, denitrochlorobenzol, nitrotoluol, nitrophenol, nitronaphthalene, etc.

Its principal use is in the coal-tar color industry and those establishments in which its intermediate products are manufactured, chief among which are chemical and pharmaceutical laboratories, perfumery, and soap factories, and in explosive works.

"Its mode of entrance into the body: (1) Absorption takes place first of all, through the skin, both the uninjured and especially the pathologically altered skin, particularly in the case of profuse perspiration; (2) through the respiratory organs; (3) through the digestive organs.

"Symptoms of Poisoning. Poisoning by all of the designated substances is pretty nearly the same, qualitatively; quantitatively, however, differences exist, so that the larger proportion they con-

[1] Industrial and Personal Hygiene, p. 46.
[2] Manual of Toxiology, 2d edition, 1912, pp. 1212 et seq.

tain of the nitro (NO_2) groups the more virulent they are likely to be. The nitrochloric compounds are very much more dangerous than the simple nitro compounds. The first toxic symptoms may appear within a few hours (8 to 24) after absorption of the poison."

Acute Poisoning. (*a*) *In mild cases:* Malaise, headache, giddiness, nausea, loss of appetite, costiveness, burning sensation of the skin and mucous membrane.

(*b*) *In severe cases:* A feeling of anxiety, disturbances of sensation, like formication on the legs and furriness on the soles of the feet, ringing in the ears; disturbances of coördination (reeling gait, stammering speech), increased excitability of the reflexes, convulsions, and a state of general spasm; later, with decline of sensibility, symptoms of paralysis; vomiting; odor of the vomitus and of the exhaled breath like that of bitter almond oil; icterus of the skin; at first increased, afterward diminished activity of the heart, with lowered tension of the pulse; visual derangements (amblyopia; optic neuritis); blood viscid, brown to deep dun color; diminution of the red corpuscles and alterations in their form; in the advanced cases, formation of methemoglobin. The course of severe cases is exceptionally varied; after intermissions, exacerbations may occur, with finally a fatal result. Death may occur also in connection with deep insensibility, without other symptoms. The symptoms which point to blood changes predominate, in severe poisoning, over nervous symptoms.

Subacute and Chronic Poisoning. Icterical skin, which gradually becomes cyanotic; methemoglobin formation; symptoms of degeneration and regeneration of the red-blood corpuscles; general debility; anemia. The clinical picture is similar to that of pernicious anemia. In the urine the poisoned corpuscles are sometimes demonstrable, and finally, the presence of hematoporphyrin and of albumin.

Measures of Relief. Immediate removal from the workroom; inhalation of oxygen; artificial respiration; eventually bloodletting; stimulants, non-alcoholic; prohibition of the use of alcoholic drinks during working hours, avoidance of the same, also, outside of employment.

"A writer in the London *Lancet* states that he has known several

instances in which the vapor of nitrobenzol, as evolved from 'almond glycerine soap' scented with it has seriously affected females. A friend of his who used a cake of this soap in taking a bath fainted from the effects of the vapor set free, and was ill for some time.

"A servant boy, aged thirteen years, tasted some 'artificial essence of bitter almonds,' which had been used to scent pomatum, but finding the taste unpleasant spat it out. The family cook who made fun of him for making such a fuss about it, also tasted, but an hour later the cook felt ill, vomited, became insensible, and fell from her chair. She remained unconscious, but finally recovered, although discoloration of the skin remained for several hours.

"The boy was not affected for six hours, when he vomited, became comatose, and died ten hours after tasting the drug.

"In experiments upon animals, made by Dr. Letheby, of England, two classes of effects were noticed, either rapid coma or a slow occurrence of palsy and coma after a considerable period of inaction of the poison. Sometimes no symptoms appear for days, when suddenly the animal would be attacked with vomiting, followed by convulsions and paralysis. After this the animals generally lay for days more or less conscious before recovery or death."

Hall concludes:

1. Nitrobenzol, artificial essence of bitter almonds, and aniline in its free state are powerful narcotic poisons.

2. That although the effect may be quick and death rapid, yet the poison may remain in the system a long time without manifesting its action.

3. That both poisons are readily discovered in the dead body in cases that are rapidly fatal.

4. That in slow cases the poison may be entirely changed or eliminated, and therefore not recognizable.

5. That both appear to be changed in the body by the process of oxidation and reduction, nitrobenzol being changed into aniline, and aniline and its salts into mauve or magenta.

The following case of chronic poisoning by nitrobenzol, which has extended over a period of nearly twenty years, presents many phases of the toxic effects of the drug:

Case I.—E. K., female, aged thirty-two years, in 1894, while engaged in laboratory work that stained both hands and clothes, learned to use nitrobenzol for its "lubricating and cleansing properties." She had been warned of its dangers, but it being so useful in her work (which was a secret process) she would not desist. More and more was used, and in 1890 her bed-room was also her work-shop, with the fumes of nitrobenzol always present. Such symptoms as fatigue and exhaustion she then attributed to overwork, but which were the beginning of the toxic effects.

There were two marked effects: First, tenderness and aching of the joints. When in bed at night, there was no position in which she could place her arms to avoid a "feeling as if her elbows were being mauled." They were so sore and tender that she would awaken at intervals with the feeling that her elbows were bruised by mere contact with the bed. Second, she would awaken at times with a sensation of stricture in the throat which she attributed to the drawing back of her head. She thought she had been lying in an uncomfortable position, would rub her neck and place her head very carefully on the pillow, but it gave no relief. When in the recumbent posture, whether awake or asleep, her head was drawn back.

In 1901 muscles of the extremities weakened, "deadened," and often felt as if they were being torn apart.

In 1902 gastro-enteric symptoms now developed; she had difficulty in digesting the simplest food, and was soon emaciated, weak, anemic, and fairly exhausted.

In 1904 she cut the palm of her hand at the base of the little finger; the wound soon healed. The muscles were so affected that the ring and little fingers when closed could not be opened at will, and when forced open sprang back with a sharp snap. She now consulted me for rheumatism, but would not believe that her condition was due to something else. During the year 1905 the muscles of the other hand were similarly affected. I had frequently seen this patient during the time mentioned, had sent her away to rest, and had suspected that something in her work had caused the different attacks of varying phenomena. The symptoms now resembled those of multiple neuritis and were increasing in intensity. She soon became unable to do any work; her joints were stiff and painful; feet so stiff and painful as to impede walking; knees so contracted as to compel her to go down stairs backward; the muscles of the left knee formed a lump which made walking difficult even with the aid of a cane. The tendency in the hands and arms was to stiffen at the joints,and to remain in the last position into which they were forced. The left side was more affected, the left eye and left ear being greatly impaired.

In 1906 she had several severe hemorrhages which came from the pharynx and larynx, but they were not due to tubercular ulcerations.

In 1907 she had general erysipelas, phlegmonous in character, and lasting several weeks. This infection had a beneficial effect upon chronic

nitrobenzol poisoning. When she recovered from the many abscesses, all of the symptoms which had been attributed to the drug had disappeared, and have not returned (after five years), although she has continued her laboratory work under certain restrictions in the use of the drug.

The recital of the treatment in detail in this case would be of little interest; however, the removal of the cause, after its late discovery, demonstrated the fact that the inhalation of the fumes of the nitrobenzol had been directly responsible for the numerous ailments. Her persistent denial of the possible influence of anything deleterious in her work often led to the belief that the symptoms were hysterical. It was only after persistent attempts to induce her to name the chemicals she used, and only after she was incapacitated for work by pain and muscular stiffness and weakness, would she confess that she used a large quantity of nitrobenzol.

When she was able to return to work (1904) she had a flue constructed by which the fumes were drawn into the chimney directly from the vessel into which the nitrobenzol was poured. For a time this worked well, but ere long new symptoms arose. Still another improvement was made which kept her from inhaling the fumes, enabling her to use the drug several hours daily without any apparent deleterious effect.

In the following 15 cases the drug was taken into the mouth.

Case II.[1]—A clerk in a chemical laboratory applied a drop or two of nitrobenzol upon his tongue to take away the odor of a pipe, which he had been smoking; and repeated it in one and one-half hours later. Feeling sick after the first dose he took an alcoholic stimulant, but an hour after the second drop a physician was called. A few hours later he had convulsions, followed by coma lasting six hours. He gradually regained consciousness, but died fifteen hours later.

Case III.[2]—Male, aged forty-seven years, drank some liquid from a bottle which he found and which was proved to be nitrobenzol. Marked cyanosis, temperature, 97° F.; pulse, 130; respiration, 30; semiconscious; marked prostration; blood chocolate colored, thick and viscid. Treatment stimulants and oxygen. Recovery, cyanosis disappearing in three days.

Case IV.[3]—Mrs. F., aged twenty-seven years, took "spurious" oil of bitter almonds. Comatose; cyanotic; almost pulseless when admitted to hospital. Recovery in two weeks.

Case V.[4]—Cook tasted of bottle containing nitrobenzol. Soon felt unwell and complained of palpitation; vomited; became insensible and fell to floor. Face puffed and leaden hue; pulse feeble; recovery.

[1] Taylor, Guy's Hospital Reports, 1864, x, 192.
[2] Boston Med. and Surg. Jour., 1905, clvi, p. 203.
[3] Stone, W. J., Jour. Amer. Med. Assoc., 1904, xliii, 977.
[4] Barham, same journal as above case.

CASE VI.[1]—Child ate tapioca containing oil of almonds. Convulsions. Recovery.

CASE VII.[2]—Man, aged twenty-one years, nitrobenzol given instead of oil of bitter almonds in prescription. 23 minims of nitrobenzol was taken. Became pale and weak. Headache; became unconscious; cyanosis; pulse could not be felt; lower jaw rigid; limbs flaccid; pupils widely dilated. Recovery.

CASE VIII.[3]—Man, aged fifty years, soap merchant. Tasted liquid used in making soap; one ear became black, and later other ear became black. Cyanosis; skin clammy; odor of bitter almonds on breath; resp. irregular; comatose; pupils dilated. Recovery.

CASE IX.[4]—Male, aged forty-eight years, had taken 2 drams of nitrobenzol into his stomach two hours before it was washed out; cyanosis; coma; involuntary micturition. Recovery in six days.

CASE X.[5]—Woman, aged thirty years. Tasted a liquid which had been used for flavoring pastry. Spat it out and washed mouth. Spilled some on table and room became filled with vapor. Burning in mouth; feeling of faintness; eyes bright and glossy; features pale and ghastly; cyanosis; feeble pulse; skin clammy; muscles rigid; respiration jerky. Recovery.

CASE XI.[6]—Male, white, aged twenty-one years. Nitrobenzol by mouth, amount unknown, marked lividity of face; pupils widely dilated; vomited matter smelled of almonds. Death about seven hours after taking.

CASE XII.[7]—Male, aged seventeen years, took one mouthful out of a bottle of nitrobenzol. It was taken about noon when his stomach was empty. Some symptoms developed in about five hours. Headache; weak pulse; cyanosis; discoloration of skin, which lasted several days; urine dark. Recovery.

CASE XIII.[8]—Male, aged sixty-four years, took a small amount of nitrobenzol by mouth; cyanosis, semi-coma; asphyxia, requiring artificial respiration for several hours; odor of oil of bitter almonds on breath. Recovery in two days.

CASE XIV.[9]—Man, aged forty-seven years, took 2 drams of nitrobenzol; vomited; looked ill; answered questions in drawling manner and seemed rather deaf. Extreme cyanosis; complexion pale and livid; skin clammy; pulse feeble; respiration shallow and irregular; jaws were tightly fixed; pupils mostly contracted. Recovery.

[1] Stralter, Med. Times, vol. ix, p. 625.
[2] Stevenson, Guy's Hospital Report, vol. xxi, p. 371.
[3] Dean, Med. Bull., 1879 and 1880, vol. i and ii.
[4] Hodson, Lancet, London, 1891, i, 877.
[5] Taylor, Guy's Hospital Reports, 1864, x, 192.
[6] Vizard, Lancet, London, 1906, i, 88.
[7] Gregory, Lancet, London, 1906, i, 1242.
[8] Courmont, La Province Méd., 1897, xi, 436.
[9] Dodd, British Med. Jour,. 1891, i, 849.

Case XV.[1]—Young man took drink of nitrobenzol by mistake. Drank salt water and vomited freely. Became weak, cyanotic and collapsed. Pulse weak, pupils dilated, unconscious; tonic spasms of all flexor muscles at times. Odor of bitter almonds in breath. Recovery.

Case XVI.[2]—Boy, aged seventeen years, while drawing off some nitrobenzol with a syphon, swallowed a portion of liquid. No immediate symptoms; felt sleepy; two to three hours later fell into stupor which became deeper and deeper until death. No vomiting or convulsions. Death.

The following 6 cases were due to the inhalation of nitrobenzol:

Case XVII.[3]—Male, aged twenty-five years, had inhaled the odor of roburite for two days. First taken with severe headache; next day, convulsions; coma; cyanosis; dyspnea; respiration shallow, sighing, almost imperceptible; urine dark; lividity lasted a week, and dyspnea ten days. Recovery.

Case XVIII.[4]—Man, aged forty-three years, spilled a quantity of nitrobenzol on his clothes and went about several hours breathing an atmosphere saturated with the vapor; gradually face became flushed; expression stupid; gait unsteady; appeared like a person who had been drinking; stupor increased to coma and in this state he died. Death.

Case XIX.[5]—Boy, aged sixteen years, scrubbed the inside of an analine vat and breathed an atmosphere saturated with vapor of nitrobenzol. Felt giddy and lapsed into unconsciousness; skin cold and clammy; pulse slow and almost inperceptible; cyanosis; breathing heavy. Recovery.

Case XX.[6]—Clerk in chemical and paraffin works used nitrobenzol to remove smell of paraffin from clothes. Touched tube to tongue to remove odor of pipe and swallowed 2 or 3 drops. Face became cyanosed, skin cold, resp. short and quick and felt like suffocating. Great oppression in chest; confusion in head; tetanic convulsions; coma; death.

Case XXI.[7]—Poisoning from inhalation of fumes of nitrobenzol. Male, aged twenty-five years, worked in a factory in which drug was used; was suddenly taken with marked cyanosis; respiration 32 (Cheyne-Stokes); pupils reacted to light; urine highly colored; odor of oil bitter almonds on breath. Recovery in three days.

Case XXII.[8]—Male, aged ?, was made ill by inhaling fumes of nitrobenzol. Great cyanosis, pulse 160, full; respiration 36; odor of drug on

[1] G. W. Maser, Med. Record, 1884, xxv, 711.
[2] McKenzie, Med. Times, 1862, i, 239.
[3] Jamieson, Australasian Med. Gaz., 1891 and 1892, xi, 355.
[4] Letheby, Guy's Hospital Reports, 1864, x, 195.
[5] Ibid.
[6] Letheby, Clinical Lecture and London Hospital Reports, vol. ii. p. 34.
[7] Reynolds, Med. Chronicle, Manchester, 1889, ci, 140.
[8] Thompson, British Med. Jour., 1891, i, 801.

breath; coma when *at rest*, urine dark, odor of nitrobenzol. Recovery in four days but discoloration of skin persisted for some time.

Two cases in which the drug was believed to have been absorbed by the skin:

Case XXIII.[1]—A strong young man, weight, 160 pounds, purchased a pair of shoes at a sale a few days before his death. The shoes had tan cloth uppers and patent leather lowers. Desiring to wear them later to a dance, he blackened the uppers with a liquid shoe-blacking. He wore the shoes before the tops were quite dry and his feet and ankles were stained. About midnight, while in a café with some friends, as he was putting on his coat, he suddenly fell to the floor unconscious. A physician was called and he was removed to his home, where he died three hours later.

The autopsy showed that death was due to the absorption of nitrobenzol, used as a perfume in the shoe-blacking.

Case XXIV.[2]—Girl, aged nine and one-half years, had used a hair lotion for phthiriasis. Apparently dead when first visited; livid; comatose; pupils dilated; vomiting; odor of bitter almonds; trismus. Recovery in twenty-four hours.

Two cases in which the drug was taken with suicidal intent:

Case XXV.[3]—Female, aged twenty-five years, attempted suicide by taking about 5 c.c. of mirbane oil with tincture of cinnamon. Reached hospital four hours later. Unconscious; markedly cyanotic; pupils normal but fail to react; pulse scarcely palpable; respiration rapid, shallow, stertorous; trismus marked, teeth firmly pressed together; breath has a decided odor of bitter almonds; later: skin and mucous membrane, blue-green; respirations short and rapid; expiration prolonged; temperature 25° C.; tetanic convulsions; 400 c.c. urine drawn, acid, dark brown, and ¼ per cent. albumin. Conscious at 4 P.M.

Two days later: jaundice; hemorrhage from genitals; urine, albumin and red corpuscles. Recovery in two weeks.

Case XXVI.[4]—Minna, aged seventeen years, attempts suicide by taking one drachm of nitrobenzol. Vomited one hour after taking it and was admitted to the hospital after five hours. Cyanosis; somnolence; vertigo; headache; urine; high sp. gr. albumin. Recovery in a week.

[1] Stone, W. J., Jour. Amer. Med. Assoc., 1904, xliii, 977.
[2] Steine, Nev. Méd. de l'Inst, 1905, xxxvii, 444.
[3] Schild, Berlin. klin. Woch., 1905, xxxii, 186.
[4] Ibid.

Three cases in which the nitrobenzol was taken to induce abortion:

Case XXVII[1].—Adelheid, aged twenty-two years, admitted to hospital October 24, 1885. Drowsy, cyanotic, almost pulseless. Respiration rapid; pupils contracted, do not react; odor of bitter almonds on breath.

October 25. Awakes suddenly; admits taking nitrobenzol to interrupt pregnancy; respiration, 36; pulse, 120; temperature, 37.5° C.; urine contains large amount of albumin, red and white corpuscles.

October 26. Passed fetus 3 inches long.

October 27. Marked jaundice; liver and spleen enlarged. Recovery in one month.

Case XXVIII.[2]—Marie, aged twenty-eight years, took 16 c.c. nitrobenzol to bring on abortion. Found unconscious; cyanosis; pupils do not react. Death six hours after taking drug.

Case XXIX.[3]—Frederica, aged twenty-four years, took 16 c.c. nitrobenzol to induce abortion and was found in toilet two hours later unconscious; cyanotic; pupils do not react; weak pulse; rapid respiration; odor of bitter almonds. Next day less cyanosis; rapid pulse; fever; headache; menstruating; jaundice. Recovery in one week.

The following instances of poisoning are given by H. O. Hale, but we have not been able to find the cases:

"One remarkable instance of aniline color poisoning was observed a short time ago in a work-house infirmary where no less than ten infants were observed to be affected with a disease which caused them to turn a peculiar bluish color. Investigation failed to throw any light upon the cause of the strange disease. The following year, about the same time, seven more infants became affected in the same manner, and it was discovered that upon the flesh of one of the infants was a faint reproduction of the stencil mark upon the napkin which the child was wearing. This aroused suspicion, and it was found that all the children who were ill were wearing new unwashed garments, which had been recently purchased and marked with the stamp of the infirmary. The nurses recalled the fact that just about the time the first ten children were taken ill the previous year, new napkins had been purchased, stamped, and used without previous washing. Thus it was proved that the aniline color used for stamping the clothing had caused the illness in the children.

[1] Schild, Berlin. klin. Woch., 1905, xxxii, 186. [2] Ibid. [3] Ibid.

"Another instance was that of a child, aged seven years, who had gotten hold of an aniline blue pencil. His hands were stained, the coloring matter got in his eyes, causing keratitis. The sclerotics were purple.

"A 'longshoreman was at work in the hold of a vessel when a package of nitrobenzol fell and broke, some of it getting on his clothing. He complained that the 'stuff' smelled very strong, but continued to work. He did not complain of being sick until after he returned from dinner. He soon began to feel dizzy and heavy, and his fellow workmen noticed that he looked very pale and blue. He drank some brandy but could not retain it. His face was pale and greenish. Recovered."

I wish to acknowledge, with thanks, the assistance given by Drs. Willson, Ong, and Gottbarth. They looked up the literature and picked out the cases.

METABOLISM OF SCURVY IN AN ADULT

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INTRODUCTION

This study was undertaken for two reasons: First, we wished to determine whether it were possible to make an accurate study of the metabolism of a rational bed patient in the hospital ward available to us without the assistance of a special nurse. Secondly, to determine whether or not a study of the mineral exchange would yield any information of value concerning scurvy, a disease which may be eventually regarded as a disturbance of metabolism.

Our first question can be answered in the affirmative. If an intelligent ward nurse, an interested interne, and the usual hospital facilities are available, a metabolic experiment such as the one described by us is possible.

The methods employed were for the most part tested on standard solutions and modified when necessary to meet experimental conditions and increase their accuracy.

LITERATURE

An exhaustive study of the *Index Medicus* and *Surgeon General's Catalogue,* as well as the special Centralblätter for biochemistry, medicine, and pediatrics, yielded little or no information of value. Most of the literature on this subject deals with the much mooted etiological question, but has no bearing upon our paper. Except for various contradictory statements by the older writers as to the

commoner mineral and organic constituents of the urine, nothing of any moment could be found. Garrod,[1] in 1848, found that anti-scorbutic articles of food were richer in potassium than ordinary food material, and that the urine and blood of scurvy patients contained a diminished amount of potassium salts.

Ralfe,[2] shortly after, though confirming the potassium deficiency in the scorbutic's urine, refuted this potassium food deficiency hypothesis by administering potassium nitrate to scurvy patients without beneficial results. This author's study is spoiled for our purposes owing to the fact that the food was not measured or analyzed. He, however, studied in the urine the free acidity, urea, uric acid, and the inorganic constituents chlorine, sulphuric acid, calcium, and magnesium phosphates, potassium and sodium phosphates, and potassium and sodium. Ralfe found in the urine of scurvy that there is an increase of uric acid, a diminution of the total acidity, and a reduction of the alkaline phosphates.

Buzzard[3] tried to overcome Ralfe's objection by stating that it was the organic salts of potash that possessed the antiscorbutic powers. More recently Hutchison[4] has accepted Buzzard's view and found that a sterilized dialysate of orange juice and to a less degree a solution of malate or tartrate or citrate of potassium had a curative effect. Litten[5] writes that the results of the potassium analyses of the urine are very contradictory; further, that phosphoric anhydride is increased, and that beyond a doubt the uric acid content is very high at the height of the disease, but diminishes rapidly with the convalescence.

Wright[6] maintained that the exclusive feeding with certain foods (as oats, barley, fresh and salt meats) which after incineration left an acid ash, were responsible for the production of scurvy, and accordingly regarded it as an acid intoxication.

Holst,[11] Frölich,[7 8 9] and Fürst[10] disproved Wright's contention by producing scurvy in guinea-pigs with foods (as peas, almonds, and lentils) yielding an alkaline ash. The disease picture both macroscopically and microscopically revealed the characteristic changes of the osseous system found in scurvy-rickets of children. Mixtures of nine varieties of dried vegetables with an alkaline ash caused scurvy in from twenty-seven to thirty-one days. In

the fresh state these vegetables possessed antiscorbutic properties. This experimental scurvy could be cured by the administration of barley, peas, and lentils which had previously been allowed to sprout. Further, raw milk lessened the scurvy produced in guinea-pigs by the exclusive feeding with oats; this antiscorbutic quality of the milk was destroyed by heating to 100° C. for ten minutes. The authors therefore concluded that scurvy is due to an absence in the food of some constituent possibly of the nature of an enzyme.

Nowhere in the literature could we find an accurate study of the mineral metabolism in a case of adult or infantile scurvy. Hence we believe that our careful study may prove of some use and stimulate future investigation.

CLINICAL HISTORY

M. M., aged thirty-eight years; laborer; Austrian Pole; admitted to Dr. H. A. Lafleur's service in the Montreal General Hospital on July 2, 1909.

Entrance Complaint. "Sore knee."

Family History. Negative.

Personal History. The patient was born in Austrian Poland where he had lived until 1907, when he emigrated to Canada. He had always enjoyed good health and denied all acute infections as scarlet, typhoid, and rheumatic fevers, syphilis, or purpura. For some months prior to his illness he had been working as a day laborer in Blue Bonnets, a little village on the outskirts of Montreal. He lived in a shanty with twenty-one other men, in one sleeping room, under poor hygienic conditions. Their food consisted of fresh meat and beans, but very little if any fresh vegetables; very little salt pork or fish were used. As far as the patient knew, none of his companions had sore gums or spots on the skin similar to his.

Present illness began one month before admission, when he had pain, swelling, and limitation of movement of the left knee-joint, which he assigned at first to an injury received three months before, which, however, had not laid him up at that time. Coincident with the swelling of the knee he noticed for the first time,

spots on the skin of the thighs as well as soreness of the gums. There were no hemorrhages from the mucous membranes or other joint symptoms.

Physical examination on July 3, 1909, revealed a fairly well-nourished, though somewhat anemic man of about stated age. Numerous petechiæ were seen around the hair follicles of both extremities, especially on their anterior surface. There was a large subcutaneous purplish ecchymosis behind the lower third of the right thigh and knee-joint, which on palpation was markedly indurated and slightly tender. The left knee-joint was much swollen, painful on movement, and of a purplish-red color. A skiagram was negative for periosteal or other bone lesions of that locality. On the outer side of the right elbow-joint was a small subcutaneous ecchymosis. In addition there were numerous small superficial ecchymoses, some quite fresh, over the posterior and inner surfaces of the left thigh. On the trunk were a few acneiform papules. Just below and to the outer side of the left elbow-joint was a subcutaneous nodule the size of a large bean. The gums, which bled very easily, were of a dull purplish hue, and very spongy; they protruded slightly over the teeth, between which they showed the usual tongue-like projections. There were two or three dark greenish-black patches of necrosis on the buccal service of the gums. The breath was distinctly fetid. The teeth were carious but not loose. The lymphatic glands were normal except for a slight enlargement of both axillary groups.

The other viscera were normal.

There was a moderate secondary anemia (hemoglobin, 40 per cent., Sahli; red corpuscles, 2,690,000), while the leukocytes were below normal (4480).

The temperature ranged between $97\frac{4}{5}°$ and 100° F. and the pulse between 80 and 90 per minute. He weighed on admission $137\frac{1}{2}$ pounds. The urine was yellow in color, acid in reaction, with a specific gravity of 1008, and contained neither albumin, sugar, nor pathological sediment.

Treatment. On July 4 the patient was placed on a special diet for purposes of study. One week later orange-juice was added to the diet.

The metabolism experiment ceased July 17, when he was found to weigh 132¾ pounds. After this he was given a general ward diet, with abundant green vegetables, lemons, and oranges. The improvement in his general condition was rapid. The gums became smaller and of a more healthy color. The brawny induration of the right thigh cleared up, and the knee-joint could be easily flexed and extended. The purpuric spots became smaller, and were represented for the most part by brownish pigmented areas. On July 23, after being up and about the ward for two days, he insisted on going home and was, consequently, discharged.

CHEMICAL METHODS

Owing to the semiliquid consistency of the stools, it was impossible to accurately separate the feces by means of charcoal, carmine, etc. For this reason the experiment was divided into four periods. The feces of the first day of the fore period and of the first two days of the main period of the experiment were collected and analyzed separately. During the first and second periods, lasting one and five days respectively the patient received the following diet, qualitatively similar to that recommended by Folin.[12] (This diet more than fulfils the requirements of the average man of 70 kilos as far as protein and calories are concerned.)

	Gm. or c.c.
Whole milk	625
Cream (18 to 22 per cent.)	375
Eggs (white and yolk)	560
Horlick's malted milk	250
Sugar	25
Sodium chloride	7
Water to	2500

The mixture was freshly prepared and 2000 c.c. administered each day. The balance was accurately measured and preserved under 20 c.c. toluol in bottles with well-fitting ground-glass stoppers. These were kept constantly in a refrigerator. During the third and fourth periods, lasting two and five days respectively the same diet was administered, except that 200 c.c. of the water were replaced by 200 c.c. of orange-juice. A sample of each day's food was analyzed separately.

The urine was collected in the ordinary hospital urinal, and transferred quantitatively by means of a known quantity of distilled water into a 2.5-liter glass-stoppered bottle, and preserved in the refrigerator under toluol. At the end of two years the urine was acid and free from bacterial growth. On analysis the urine was found to contain, in addition to a rather bulky sediment of urates, a relatively heavy one of uric acid. In order to obtain a clear solution, we proceeded as follows: The bottle was thoroughly shaken and about 500 c.c. of the urine quickly transferred into a

dry round-bottomed flask, the neck of which was drawn out into a tube about 70 cm. long and 12 to 13 mm. in diameter. This tube was surrounded by a glass condensing jacket and cooled with running water. The urine could now be heated to boiling without loss of water, which was necessary at times in order to obtain a clear solution, and even then a few crystals of uric acid would remain undissolved. The urine in the flask was afterward rapidly cooled to 15° C., and transferred to a dry Jena Erlenmeyer flask, and the required volume pipetted.

The total nitrogen, the ammonia, and the total acidity were

determined in the freshly collected and unheated urine at the outset of the experiment.

The mineral ingredients were analyzed subsequently at our leisure. We would here advise that for the preservation of the urine for potassium and sodium analyses, bottles made of Jena or other resistant glass be used.

The stools for each period were transferred quantitatively by means of distilled water into a carefully tared desiccator, and dried to constant weight *in vacuo* at 45° to 55° C. The desiccator was placed in a water-bath and connected by means of a curved glass tube with a 2-liter distilling flask, the stem of which entered a suction flask containing a little $\frac{N}{10}$ H_2SO_4 solution and a drop of alizarin red. The diminished pressure was obtained by means of an ordinary water suction apparatus and the condensation by means of running water.

In this way the feces were dried to constant weight in twelve to thirty-six hours, depending on the quantity. On the average, 5.7 per cent. of the total nitrogen present in the feces was found in the clear distillate. Frothing of the feces was prevented by aëration through the small tube and a few drops of petroleum. The total quantity of the dried feces was obtained by subtracting the weight of the empty desiccator from the desiccator and dried feces. The bulk of the feces was removed with a spatula, ground in a mortar, and preserved in bottles hermetically sealed with paraffin until analyzed. It was not necessary to pulverize the feces, as concordant duplicate analyses were obtained with samples containing particles the size of a pea. For example, the following results for nitrogen and calcium were obtained:

	Amount gm.	Nitrogen	Calcium
Feces I[1]	1	0.0273	0.0790
	1	0.0269	0.0787
Feces II	1	0.0622	0.0441
	1	0.0626	0.0445
Feces III	1	0.0509	0.0564
	1	0.0509	0.0573
Feces IV	1	0.0427	0.0667
	1	0.0425	0.0665

[1] The analyses were carried out in duplicate.

The homogeneous nature of the liquid food mixture employed was determined by repeated analyses of definite volumes.

Analytical Methods. All analyses were carried out in duplicate and rejected unless the variation between the two analyses was well within the experimental error. The average of the duplicate analyses was selected as the basis for calculation. The maximum variation for each series is given in its proper place. It was computed by selecting the greatest variation between the duplicates of a series and this error calculated for 100 c.c. of urine or food or 100 grams of feces.

Urine. The *nitrogen* was determined according to Kjeldahl, 10 c.c. being used in duplicate. Sodium alizarinsulphonate was used as indicator. The maximum variation for 100 c.c. urine was 0.004 nitrogen.

The *ammonia* was determined according to Folin,[13] 25 c.c. being used and the air passed through the cylinder over night. The indicator used was sodium alizarinsulphonate. The maximum variation between the duplicates for 100 c.c. of urine was 0.003 NH_3.

The *total acidity* was estimated according to Folin.[14] The number of cubic centimeters of $\frac{N}{10}$ Na(OH) required to neutralize the total quantity of the urine was calculated. The exact end-point in this titration could only be accurately determined after a good deal of experience, the yellow color of the urine obscuring the indicator, phenolphthalein. The maximum variation was 0.8 c.c. $\frac{N}{10}$ Na(OH) for 100 c.c. urine.

The *total sulphur* was determined according to Benedict[15] with 10 c.c. of urine. This method was found to be more accurate and rapid than the sodium peroxide method used by Folin.[16] The following consecutive analyses are illustrative:

	$BaSO_4$, gm.
July 4	0.1000
	0.1000
July 5	0.0924
	0.0930
July 6	0.0944
	0.0946
July 7	0.0921
	0.0923
July 8	0.1031
	0.1030

The maximum error in duplicate determination was less than 0.001 gram sulphur for 100 c.c. urine. We did not, therefore, find it necessary to use the modification suggested by Denis.[17]

Chlorin was estimated according to Clarke's[18] modification of Dehn's method, 10 c.c. of urine being used in duplicate. The maximum error was 0.004 gram Cl in 100 c.c. of urine.

Total Phosphorus. The urine was first ashed according to Neumann in Kjeldahl flasks of Jena glass. Five cubic centimeters of concentrated H_2SO_4 was added to 100 c.c. urine, and complete destruction of the organic matter obtained by the gradual addition of concentrated nitric acid. The ash and sulphuric acid were transferred to a measuring flask and diluted to 250 c.c. This solution served for the determination of the total phosphorus as well as the potassium and sodium. Twenty-five cubic centimeters of this solution, corresponding to 10 c.c. of urine, were analyzed according to the volumetric method of Neumann[19] for phosphorus. In order to obtain a coarsely granular precipitate of the ammoniophosphomolybdate which might be easily washed free of acid and filtered, we proceeded as follows:

To 25 c.c. of the Neumann ash solution in a Jena Erlenmeyer flask of 400 c.c. capacity, 125 c.c. of water, 50 c.c. of 50 per cent. ammonium nitrate solution, 3 c.c. of concentrated sulphuric acid, and 1 c.c. of concentrated nitric acid were added. The mixture was then heated until bubbles began to appear, and then precipitated with 40 c.c. of 10 per cent. ammonium molybdate solution. The flask was then shaken until precipitation was complete (about one minute) and allowed to stand for ten minutes, after which it was decanted through Gooch crucibles in the manner suggested by Bayliss and Plimmer.[20]

As a rule, after four washings the precipitate was free from acid and could then be decomposed and titrated in the usual manner. In this way the total phosphorus of the urine, feces, and food could be rapidly and accurately determined. As many as three duplicate determinations were carried out on the ash solution in ten hours. The following five consecutive duplicate analyses illustrate the accuracy of this method:

	P_2O_5, gm.
July 12	0.0398
	0.0400
July 13	0.0406
	0.0407
July 14	0.0408
	0.0408
July 15	0.0414
	0.0420
July 16	0.0398
	0.0395

The maximum error was 0.005 gm. phosphorus for 100 c.c. urine.

Sodium and Potassium. These were determined on the Neumann ash solution mentioned above. Twenty-five cubic centimeters of the solution (equivalent to 10 c.c. urine) were evaporated in a platinum dish and the sulphuric acid completely volatilized. The residue was dissolved in a little distilled water, transferred to a Jena Erlenmeyer flask to which was added 5 c.c. of concentrated HCl and 100 c.c. of water; this solution was now boiled and the SO_4 ions were precipitated by the gradual addition of barium chloride through the Folin automatic dropper.[21] When cool the barium sulphate was filtered off through an ashless filter into a platinum dish; the precipitate was now washed thoroughly and the washings and filtrate evaporated to dryness on the water-bath to remove the bulk of the hydrochloric acid. The residue was again dissolved in water, transferred to a Jena Erlenmeyer flask, to which 100 c.c. of water was added, then heated to boiling and precipitated by the gradual addition (drop method) of 20 c.c. of a half-saturated solution of chemically pure barium hydrate obtained by double recrystallization. When cold it was filtered and washed thoroughly. The filtrate and washings were treated with an ammoniacal solution of ammonium carbonate (made by passing dry CO_2 into a 15 per cent. solution of NH_3) until no further precipitation occurred. After two hours the precipitate was then filtered off, washed thoroughly, and the filtrate and washings evaporated carefully to dryness on the water-bath, avoiding a too rapid decomposition of the ammonium carbonate. The residue was again treated with about 10 c.c. of the ammoniacal ammonium carbonate solution for two hours, any resulting precipitate filtered, and the filtrate and washings again evaporated to dryness. The residue was taken up in water, trans-

ferred to a weighed platinum crucible, evaporated to dryness on the water-bath and the ammonium salts volatilized. When the weight of the crucible was constant, the weight of the chlorides of the potassium and sodium was noted; they were then dissolved in a little water and filtered, as a small amount of insoluble residue was always present. The filter and residue were washed thoroughly, dried, and incinerated, and the weight of the ash deducted from the weight of the sum of the chlorides of potassium and sodium.

The potassium was determined as potassium platinic chloride (K_2PtCl_6). In this way acceptable results were obtained with a standard solution containing potassium and sodium chloride, acid potassium phosphate, sulphuric acid, calcium carbonate, and magnesium sulphate in about the proportions in which they occur in the ash solution to be analyzed.

	NaCl, gm.	KCl, gm.
Solution I contained	0.1011	0.0692
Solution I found	0.1016	0.0694
Solution I found	0.1003	0.0691
Solution I found	0.1016	0.0694
Solution II contained	0.0809	0.0553
Solution II found	0.0806	0.0552
Solution II found	0.0814	0.0550
Solution II found	0.0811	0.0553

The maximum error for sodium was 0.005 and for potassium 0.009 for 100 c.c. of urine.

Calcium and Magnesium. Fifty cubic centimeters of urine were analyzed directly for calcium and magnesium according to the method of McCrudden.[22] We can fully corroborate the author's claim for the accuracy of his method. For seven consecutive duplicate analyses we obtained the following:

	MgO, gm.	CaO, gm.
July 4	0.0107	0.0117
	0.0107	0.0117
July 5	0.0074	0.0120
	0.0073	0.0122
July 6	0.0069	0.0129
	0.0072	0.0129
July 7	0.0069	0.0123
	0.0072	0.0125
July 8	0.0087	0.0142
	0.0088	0.0146
July 9	0.0080	0.0146
	0.0080	0.0146
July 10	0.0078	0.0141
	0.0078	0.0141

The Aron[23] method for determining calcium as $CaSO_4$ proved entirely unsatisfactory in our hands.

2. *Food.* For the *total nitrogen* 5 c.c. was taken in duplicate and determined by Kjeldahl's method.

For the *total sulphur*, 5 c.c. was also taken and determined by Benedict's method with the following results:

	$BaSO_4$, gm.
July 8	0.0228
	0.0228
July 9	0.0226
	0.0222
July 10	0.0216
	0.0220
July 11	0.0224
	0.0228
July 12	0.0206
	0.0213

The maximum error was 0.003 gram of sulphur for 100 c.c. of food.

The total *chlorin* was determined in duplicate, using 5 c.c. of food. The sodium peroxide method was used and chlorin weighed as silver chloride (AgCl). The maximum error was 0.006 gram of chlorin for 100 c.c. of food.

The *phosphorus* was determined in 100 c.c. of the food by ashing according to Neumann and the ash and sulphuric acid diluted to 250 c.c. Of this solution 25 c.c. in duplicate were analyzed in the manner above described. The maximum error was 0.003 grams of phosphorus for 100 c.c. of food.

The *sodium* and *potassium* were determined in the same manner as in the urine, using 25 c.c. of the ash solution or 10 c.c. of food in duplicate. The following five consecutive results were obtained.

	NaCl, gm.	KCl, gm.
July 4	0.0530	0.0351
	0.0529	0.0352
July 5	0.0499	0.0359
	0.0497	0.0367
July 6	0.0529	0.0424
	0.0530	0.0429
July 7	0.0512	0.0368
	0.0519	0.0361
July 8	0.0450	0.0360
	0.0456	0.0369

The maximum error was 0.0027 gram for sodium and 0.0057 gram for potassium for 100 c.c. of food.

The *calcium* and *magnesium* in the food were determined as follows. Twenty-five cubic centimeters of the food were allowed to dry on a platinum dish on the water-bath for from twleve to fifteen hours; it was then gradually charred and extracted with dilute hydrochloric acid. The residue was now gradually incinerated until a grayish-white ash with a few black particles remained; to this the hydrochloric acid extract was added and the whole evaporated and allowed to dry in an oven at 110° C. for two hours, to render any silicic acid insoluble. The ash was then dissolved in about 100 c.c. of water containing 3 c.c. concentrated hydrochloric acid, filtered and analyzed for calcium and magnesium by McCrudden's method. The maximum error was 0.0017 gram calcium and 0.0007 gram magnesium for 100 c.c. of food.

3. *Feces.* *Nitrogen* was determined in 10 c.c. of the distillate obtained from the feces while drying *in vacuo*, as well as in 1 gram of the dry feces. The maximum error for 100 grams of the dried feces being 0.04 gram of nitrogen.

Sulphur. From 0.5 to 1.5 grams of the dried feces were treated with 20 c.c. of fuming nitric acid in a Kjeldahl flask, and a small amount of heat applied until the solid matter had disappeared and the brown fumes had considerably decreased. The solution was then transferred to a 100 c.c. porcelain evaporating dish, to which 20 c.c. of Benedict's solution and 2 grams of C. P. sodium chloride were added; the whole evaporated to as complete dryness as possible, then very gradually heated to redness, and when cold covered with a watch-glass and dissolved in dilute HCl, filtered and precipitated in the usual manner. The four specimens examined by this method gave the following sulphur value for 1 gram of dried feces:

I	0.0043
	0.0044
II	0.0061
	0.0061
III	0.0083
	0.0084
IV	0.0040
	0.0041

Maximum error for 100 grams dried feces was 0.01 sulphur. The sodium chloride was added to prevent loss by deflagration,

which regularly occured in the trying out of Wolff and Osterberg's modification of Benedict's method.[24]

Chlorine from 1 to 1.5 grams of the dried feces was weighed into a platinum dish, 25 c.c. of a 10 per cent. solution of C. P. sodium carbonate added, and the whole evaporated to dryness on the water-bath, then gradually incinerated, avoiding red heat. The cold ash was extracted with dilute nitric acid under a watch-glass, the residue heated until white, the acid extract added, and the whole evaporated to dryness, then heated to 110° for two hours, taken up in dilute nitric acid, filtered, and precipitated with silver nitrate solution. When cold and the precipitate had settled, the silver chloride was filtered through a tared Gooch crucible, dried at 120° C., and weighed. The four samples analyzed gave the following chlorine values for 1 gram of dried feces:

	Cl, gm.
I	0.0099
	0.0101
II	0.0215
	0.0212
III	0.0150
	0.0143
IV	0.0062
	0.0060

The maximum error was 0.07 chlorine for 100 grams of the dried feces.

Phosphorus was determined according to Neumann, as in the case of the urine and food. The maximum error was 0.04 gram of phosphorus for 100 grams of the dried feces.

Sodium and Potassium. The same method was used as for urine and food. The maximum error was 0.04 per 100 grams dried feces for sodium, and 0.05 per 100 grams dried feces for potassium.

Calcium and Magnesium. Dry ashing was resorted to. The subsequent steps were identical to those previously described under the calcium and magnesium determination in the food. The maximum error for calcium was 0.028, and for magnesium 0.024 for 100 grams of dried feces.

PROTOCOLS

(See Tables I and II.)

TABLE I

Date, July, 1909.	Sp. gr. of urine 1.0— / Volume of urine.	Total nitrogen. Intake.	Total nitrogen. Output. Urine.	Total nitrogen. Output. Feces.	Total nitrogen. Balance.	Ammonia nitrogen of urine.	Ammonia nitrogen in percentage of total nitrogen.	Total acidity of urine in c.c. of $\frac{n}{10}$ sodium hydrate	Total sulphur. Intake.	Total sulphur. Output. Urine.	Total sulphur. Output. Feces.	Total sulphur. Balance.	Chlorine. Intake.	Chlorine. Output. Urine.	Chlorine. Output. Feces.	Chlorine. Balance.	Remarks.
4	23 / 865	19.42	13.82	1.17	+4.43	0.89	6.4	Not calculated	1.23	1.19	0.17	—0.13	6.95	3.33	0.40	3.22	
5	26 / 920	19.82	13.29	4.07	+2.46	0.66	4.9	477.0	1.28	1.17	0.36	—0.25	6.52	5.70	1.25	—0.43	
6	25 / 960	21.62	13.79	4.07	+3.76	0.83	6.0	521.0	1.30	1.24	0.36	—0.30	6.83	5.78	1.25	—0.20	Milk, cream, and egg diet.
7	26 / 1030	18.18	15.73	4.07	—1.62	0.89	5.7	656.0	1.25	1.30	0.36	—0.41	6.60	6.87	1.25	—1.52	
8	28 / 910	19.36	15.59	4.07	—0.30	0.89	5.7	705.0	1.32	1.29	0.36	—0.33	5.94	4.92	1.25	—0.23	
9	25 / 1070	18.53	17.91	4.07	—3.45	0.93	5.2	710.0	1.29	1.47	0.36	—0.54	6.44	6.37	1.25	—1.18	2000 c.c. p. d.
Daily average	26 / 978	19.51	15.26	4.07	+0.18	0.84	5.5	613.8	1.29	1.29	0.36	—0.36	6.47	5.93	1.25	—0.71	
Balance for period	....	....	....	....	+0.85				....	....	....	—1.83	....	....	....	—3.56	
10	25 / 1096	18.96	17.92	1.02	+0.02	0.93	5.2	743.0	1.26	1.42	0.16	—0.32	6.64	6.56	0.28	—0.20	
11	24 / 1030	19.61	15.26	1.02	+3.33	0.91	6.0	529.0	1.32	1.30	0.16	—0.14	6.31	5.94	0.28	+0.09	
Daily average	245 / 1063	19.29	16.59	1.02	+1.68	0.92	5.6	636.0	1.29	1.36	0.16	—0.23	6.48	6.25	0.28	—0.06	
Balance for period	....	....	....	....	+3.35				....	....	....	—0.46	....	....	....	—0.11	Milk, cream, and egg diet.
12	26 / 1168	19.22	17.86	1.45	—0.09	0.85	4.7	696.0	1.22	1.57	0.14	—0.49	6.16	5.85	0.20	+0.11	
13	27 / 930	19.75	14.35	1.45	+3.95	0.87	6.0	450.0	1.43	1.25	0.14	+0.04	6.94	5.11	0.20	+1.63	1800 c.c. + 200 c.c. orange-juice p. d.
14	26 / 1190	19.27	18.45	1.45	—0.63	1.11	6.0	696.0	1.36	1.66	0.14	—0.44	7.23	5.95	0.20	+1.08	
15	30 / 1080	18.98	17.37	1.45	+0.16	1.22	7.0	526.0	1.41	1.55	0.14	—0.28	6.87	6.77	0.20	—0.10	
16	30 / 990	18.45	16.85	1.45	+0.15	0.92	5.5	569.0	1.30	1.45	0.14	—0.29	6.30	5.79	0.20	+0.31	
Daily average	28 / 1072	19.13	16.98	1.45	+0.71	0.99	5.8	587.0	1.35	1.50	0.14	—0.29	6.70	5.89	0.20	+0.61	
Balance for	....	....	....	....	+3.54				....	....	....	—1.46	....	....	....	+3.03	

Table II

Date, 1909.	Total phosphorus. Intake.	Total phosphorus. Output. Urine.	Total phosphorus. Output. Feces.	Total phosphorus. Balance.	Sodium. Intake.	Sodium. Output. Urine.	Sodium. Output. Feces.	Sodium. Balance.	Potassium. Intake.	Potassium. Output. Urine.	Potassium. Output. Feces.	Potassium. Balance.	Calcium. Intake.	Calcium. Output. Urine.	Calcium. Output. Feces.	Calcium. Balance.	Magnesium. Intake.	Magnesium. Output. Urine.	Magnesium. Output. Feces.	Magnesium. Balance.	Remarks.
4	2.53	1.49	1.09	—0.05	4.39	2.56	0.24	+1.59	3.88	1.78	1.08	+1.02	1.84	0.14	2.23	—0.53	0.32	0.11	0.17	+0.04	
5	2.61	1.14	1.15	+0.32	4.13	4.03	0.80	—0.70	4.01	1.95	1.53	+0.53	1.93	0.16	1.85	—0.08	0.35	0.08	0.25	+0.02	Milk, cream, and egg diet.
6	3.23	1.45	1.15	+0.63	4.42	4.16	0.80	—0.54	4.74	2.06	1.53	+1.15	2.68	0.18	1.85	+0.65	0.36	0.08	0.25	+0.03	
7	2.61	1.75	1.15	—0.29	4.30	4.70	0.80	—1.20	4.05	2.39	1.53	+0.13	1.92	0.18	1.85	—0.11	0.29	0.09	0.25	—0.05	
8	2.75	1.79	1.15	—0.19	3.76	3.54	0.80	—0.58	4.03	2.31	1.53	+0.19	1.94	0.19	1.85	—0.10	0.31	0.10	0.25	—0.04	
9	2.60	1.95	1.15	—0.50	4.18	4.23	0.80	—0.85	4.00	3.00	1.53	—0.53	1.89	0.22	1.85	—0.18	0.33	0.10	0.25	—0.02	
Daily average	2.76	1.62	1.15	—0.006	4.16	4.13	0.80	—0.77	4.17	2.34	1.53	+0.29	2.07	0.19	1.85	+0.036	0.33	0.09	0.25	—0.012	2000 c.c. p. d.
Balance for period	....	....	....	—0.03	....	....	....	—3.87	....	....	....	+1.47	....	....	....	+0.18	....	....	....	—0.06	
10	2.59	1.90	0.47	+0.22	4.22	3.93	0.20	+0.09	4.52	3.75	0.40	+0.37	1.85	0.22	0.78	+0.85	0.32	0.10	0.10	+0.12	
11	2.66	1.53	0.47	+0.66	4.18	3.63	0.20	+0.35	4.75	3.31	0.40	+1.04	1.97	0.22	0.78	+0.97	0.37	0.12	0.10	+0.15	
Daily average	2.63	1.72	0.47	+0.44	4.20	3.78	0.20	+0.22	4.64	3.53	0.40	+0.71	1.91	0.22	0.78	+0.91	0.345	0.11	0.10	+0.135	
Balance for period	....	....	....	+0.88	....	....	....	+0.44	....	....	....	+1.41	....	....	....	+1.82	....	....	....	+0.27	Milk, cream, and egg diet.
12	2.62	2.03	0.76	—0.17	3.92	3.81	0.080	+0.03	4.45	3.90	0.56	—0.01	1.99	0.24	1.55	+0.20	0.35	0.15	0.21	—0.01	
13	2.65	1.65	0.76	+0.24	4.38	3.43	0.080	+0.87	4.56	3.32	0.56	+0.68	1.92	0.17	1.55	+0.20	0.37	0.11	0.21	+0.05	
14	2.66	2.12	0.76	—0.22	4.67	4.10	0.080	+0.49	4.62	3.49	0.56	+0.57	1.82	0.24	1.55	+0.03	0.36	0.19	0.21	—0.04	1800 c.c. +
15	2.62	1.97	0.76	—0.11	4.60	4.45	0.080	+0.07	4.97	3.71	0.56	+0.70	2.00	0.20	1.55	+0.25	0.41	0.16	0.21	+0.04	200 c.c. orange-juice p. d.
16	2.50	1.71	0.76	+0.03	3.99	3.64	0.080	+0.27	4.49	3.54	0.56	+0.39	1.95	0.18	1.55	+0.22	0.38	0.15	0.21	+0.02	
Daily average	2.61	1.90	0.76	—0.046	4.31	3.89	0.080	+0.35	4.62	3.59	0.56	+0.47	1.94	0.21	1.55	+0.18	0.37	0.15	0.21	+0.012	
Balance for period	....	....	....	—0.23	....	....	....	+1.73	....	....	....	+2.33	....	....	....	+0.90	....	....	....	+0.06	

DISCUSSION

Having selected a diet qualitatively similar to that administered by Folin[12] in his metabolic experiments on the normal man, we have the opportunity of comparing our results, to some extent, with his.

The Total Nitrogen. The nitrogen ingested was fairly constant throughout the experiment, the average daily intake ranging between 19.13 and 19.51 grams. The average daily excretion during the fore period was 15.26 grams in the urine and 4.07 grams in the feces, *i. e.*, about 21 per cent. of the total nitrogen excreted appeared in the feces. There was, therefore, a positive balance or nitrogen retention of 0.85 grams N. for the whole period During the second part of the fruit-juice period 16.98 grams were excreted per day in the urine, while only 1.45 grams (or 7.8 per cent. of the total N) were present in the feces. A more marked positive balance (3.54 grams for the period) was present after the administration of orange-juice. Laurenti[25] has recently found, following the administration of various fruit juices, an increase in the output of both the total nitrogen and the uric acid in the urine, though no mention is made of the analyses of the feces or of the food in the abstract of his paper. In our case the urine nitrogen was increased during the fruit-juice period, but this was counterbalanced by the diminution of the nitrogen in the stools.

The *ammonia nitrogen* was slightly increased, both relatively and absolutely, but no marked difference between the periods is noticeable. The average daily ammonia-nitrogen excretion for Period II was 0.84; for Period IV, 0.99, as compared with Folin's average of 0.70. The ammonia coefficient was 5.5. for Period II and 5.8 for Period IV. Folin's average was 4.3. From these data one can unquestionably exclude an acidosis, as is claimed by Wright.

The *total acidity* of the urine was somewhat lower for the fruit-juice period, 587, as compared with 613.8 for the preliminary period. Folin's average was 617, and his minimum acidity, 554.

The *total sulphur* metabolism was rather unusual. With the

exception of one day, more sulphur was eliminated than ingested. At first we attributed this result to an analytical error, but further control determinations substantiated this finding. During periods II and IV respectively an average daily loss of 0.36 and 0.29 occurred, leading to a minus balance of 1.83 and 1.46 grams of sulphur for Period II and IV respectively, whereas the nitrogen balance was positive for both periods. The daily sulphur eliminated with the feces during Period II was 0.36 gram, or 21.9 per cent. of the total. Of the sulphur eliminated during the fruit-juice period, only 0.14 gram were passed per rectum. This amounts to 8.5 per cent. of the total sulphur elimination. For want of material we were, unfortunately, unable to examine the sulphur partition.

The *chlorin* ingestion was fairly constant, 6.47 grams during Period II and 6.7 grams during period IV being the average daily intakes. The urinary chlorin excretion was practically similar for both periods, being 5.9 grams. Folin's daily average was 6.1. Here, again, we have the better utilization during the fruit-juice period, for only 0.2 gram was lost through the feces, *i. e.*, 3.1 per cent. of the chlorin eliminated, whereas during the preliminary period 1.25 grams, or 17.4 per cent. of the total chlorin excreted, was present in the feces. The average daily loss for period II was 0.71 gram, compared with an average daily gain of 0.61 gram for Period IV.

The Total Phosphorus. The average daily intake varied between 2.76 and 2.61 grams. The daily urinary phosphorus averaged 1.62 and 1.9 grams for the respective periods, while 1.15 grams was the average daily amount passed in the feces during Period II, as compared with 0.76 gram during Period IV. The balance was slightly negative throughout, 0.006 and 0.046 being the average daily losses during periods II and IV respectively.

Sodium. The average daily intake varied between 4.16 and 4.31 grams for Periods II and IV respectively. During the former 16.2 per cent., and during the latter only 1.7 per cent. was lost through the feces. During Period II the balance was negative (—3.87), equivalent to an average daily loss of 0.77 gram. During Period IV the balance was positive (—1.73), equivalent to an average daily gain of 0.35 gram.

The sodium behaved very much like the chlorin, as one would expect.

Potassium. The intake varied between the daily average of 4.17 for the preliminary period and 4.62 for the fruit-juice period. A much larger percentage of the excretion occurred through the feces than was the case with sodium. During Period II, 1.53 grams (or 39.5 per cent. of the total excretion) was the average daily amount present in the feces. During Period IV, 13.5 per cent. was lost in the feces. The balance was positive throughout, 0.29 and 0.47 gram being the average gains for Periods II and IV respectively.

Calcium. Here the excretion took place largely through the intestine, as one would expect; 0.19 and 1.85 grams was the average daily excretion in the urine and feces respectively during Period II, contrasted with 0.21 and 1.55 for period IV. The balance was positive throughout but greater during Period IV (0.90), as compared with Period II (0.18).

Magnesium. Here, again, 0.25 gram was excreted in the feces and 0.09 in the urine during period II as compared with 0.21 and 0.15 gram during period IV. The balance was negative during the former (—0.06) and positive during the latter (+0.06) periods.

CONCLUSIONS

As this is the first accurate study of the metabolism of scurvy, it would be hazardous to venture any conclusion from the above figures.

In our experiment the loss of the various food constituents through the feces was less when the fruit juice was added to the diet. The total sulphur metabolism was abnormal throughout. Chlorin and sodium were retained during the fruit-juice period, but excreted in excess of the intake during the preliminary period. More potassium, calcium, and magnesium were retained during the fruit-juice period.

If an opportunity presents, we hope to acquire additional data, and possibly substantiate the above figures. Finally, we take pleasure in thanking Prof. H. A. Lafleur for his kind permission

to study the case in his ward, and Prof. R. F. Ruttan for the use of the laboratory, and various pertinent suggestions.

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THE HEMOLYTIC ACTION OF SALTS OF FATTY ACIDS

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Since the paper published four years ago by Faust and Tallquist, in which they ascribed the anemia caused by Bothriocephalus latus to the unsaturated fatty acid, oleic acid, which the worm contains, there has been a general tendency to regard unsaturated fatty acids as possibly playing a large role in other anemias too. They showed that the saturated acid corresponding to oleic, stearic acid, was far less actively hemolytic, and that the same difference existed between the properties of certain other unsaturated acids and the saturated acids corresponding to them.

Since that time it has also become more generally familiar that oleic acid is not the only or the most unsaturated acid occurring in compounds present in the body tissues, in lecithin and other related substances in which fatty acids are associated with phosphoric acid and nitrogenous bases. It was possible that these more unsaturated acids, if liberated in the system, might develop more strongly hemolytic properties than oleic acid, and that they might in that case be particularly related to some forms of anemia.

In order to investigate this point, it was necessary to have some standard to which to refer. Oleic acid (Schuchardt) was made into the sodium soap, dissolved in methyl alcohol, and taken for this purpose. A series of tubes each containing 0.5 c.c. of a 5 per cent. suspension of rabbit's red blood cells was made up so that each tube contained a different small amount of the oleate in normal saline, and to it the total volume of fluid in each tube was brought up to 2 c.c. with normal saline. These were placed in the thermo-

stat for two hours and read, and after standing at room temperature until next day were read again. The amount of sodium oleate required to give complete hemolysis was thus determined and compared with the amount of the sodium soaps of other acids that was necessary to give it.

The substances investigated are:

1. The alcohol ether extracts of the liver and heart of a man, divided into a portion soluble and a portion insoluble in acetone.

2. The fatty acids set free from these fractions by saponification.

3. Fatty acids obtained from linseed and cod-liver oil, the former having the iodine value 180, and the latter 162; both, therefore, containing acids more unsaturated that oleic acid in larger amounts than the acids obtained from the extracts mentioned above.

4. Various saturated acids, addition or oxidation products of oleic acid; namely, the chloriodostearic acid obtained by treating foleic acid with Wijs' solution of iodine chloride, bromostearic acid ormed by treating oleic acid with hydrobromic acid; dibromostearic, acid, formed by treating oleic acid with bromine, and an analyzed preparation of dihydroxystearic acid, formed in the oxidation of oleic acid in the cold with alkaline permanganate.

5. Erucic acid (a higher member of the oleic acid series) and linoleic acid, an acid with two unsaturated pairs of carbon atoms.

The results so far obtained would show that: (1) The hemolytic power of fatty acids does not increase with the addition of further double bonds; since the fatty acids obtained from liver extracts are only one-fourth as active as oleic, although their iodine value is higher, *i. e.*, they have more double bonds; the fatty acids obtained from cod-liver oil and linseed oil were active in doses that were not smaller than the effective dose of oleic acid, linoleic acid similarly was not more strongly hemolytic than oleic. (2) The saturation of the double bonds in oleic acid by halogens, so far from diminishing the hemolytic power of this substance, leave it unaltered, and in the case of bromostearic acid, at least, seems even to increase it. The addition of two hydroxyl groups, on the other hand, in the case of dihydroxystearic acid diminishes the power of the hemolytic agent.

The quantitative results obtained so far as they are concerned

with sodium oleate seem to confirm those of previous works. Faust and Tallquist say that 1 to 5 mg. of erucic, crotonic, and cinnamic acids cause "intense or complete" hemolysis of 10 c.c. of a 2 per cent. suspension of ox red blood corpuscles in two hours at 37° C., and in "intensity of their action are equal to oleic acid." Also, they state that the sodium salts of oleic and erucic acids are as strongly lytic as the free acids; while stearic and palmitic acids caused no hemolysis of red blood corpuscles of any of the species examined when added up to any amount (beliebiger menge) as sodium salts. These statements are clearly not intended to be very exactly quantitative. But if 10 c.c. of a 2 per cent. suspension of ox red blood corpuscles requires the same amount of a lytic agent as 4 c.c. of a 5 per cent. suspension, and if rabbit's blood corpuscles are equivalent to those of the ox, then the dose given by Faust and Tallquist would be reduced to $\frac{1}{8}$ to $\frac{1}{2}$ mg. for the quantities of red blood corpuscles used in the experiments here reported. The dose actually found was $\frac{1}{40}$ to $\frac{1}{25}$ of a mg.

Noguchi, also using ox red blood corpuscles, determined the minimum lytic dose of sodium oleate for 2 c.c. of a 5 per cent. suspension to be 0.07 mg.; for $\frac{1}{2}$ c.c., therefore, this would be reduced to 0.018, and in the case of the rabbit the figure actually found was 0.024 mg., a variation of only about 40 per cent., which is hardly beyond the limits of experimental error in such experiments as these. He found that sodium stearate had to be added in seven times this amount to give complete hemolysis—a result closely comparable again to our results in the case of palmitate and dioxystearate.

Solutions of sodium oleate and dibromostearate of the same molecular concentration were found to be hemolytic for the blood corpuscles of the ox, sheep, rabbit, and man, in the same dose, the corpuscles of these four species, the only ones so far tested, being therefore equally sensitive to the action of both these hemolytic substances. Moreover, the dose required for complete hemolysis of the corpuscles obtained from a case of pernicious anemia were the same as that for samples of blood from two normal human subjects.

The inhibitory action of the serum of a rabbit upon hemolysis of its corpuscles by sodium oleate was stronger than upon that by

dibromostearate; in the former case 0.001 c.c. inhibited the effect of the minimal dose, in the latter 0.01 c.c. was necessary.

Finally, experiments have been undertaken and are still in progress with a view to determining whether after hemolysis of blood corpuscles with sodium dibromostearate the soap can be shown to have combined with the stroma in effecting the hemolysis. If that is the case the washed stroma should yield an ash containing bromine; strictly, indeed, when no more than the minimum amount of the soap necessary for complete hemolysis has been used the whole of the bromine it contained should be so found. The final result of these experiments and the discussion of the interpretation to be put upon them will be published, it is hoped, at an early date.

PANCREATIC TRANSPLANTATIONS IN THE SPLEEN[1]

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It is now acknowledged by all authorities that total removal of the pancreas produces diabetes. Minkowski[2] found, however, that the presence of a subcutaneous transplant of a portion of the pancreas would prevent the development of diabetes provided the blood supply of the graft was left intact.

The lower part of the pancreas in the dog lies free in the mesentery. This has been named by Pflüger[3] the processus uncinatus. This portion of the gland joins above the corpus pancreatis which is in close contact with the duodenum. Into the lower end of the processus uncinatus enter goodly sized vessels, branches of the inferior duodenal artery and vein. Minkowski cut through the processus uncinatus in its upper part. The portion of the pancreas thus freed was drawn out of the abdomen and placed in a prepared pocket in the subcutaneous tissue. The bloodvessels entering the tip of the gland were carefully preserved. They formed a vascular stalk which passed from the peritoneal cavity through the incision in the anterior wall of the abdomen to the graft. The external secretion of the gland was discharged through a fistulous opening

[1] Investigation made with the aid of a grant from the Proctor Fund for the study of chronic disease.

[2] Berliner klin. Wochenschrift, 1892, No. 5; Verhandlungen, XI Congress für innere Medizin, Wiesbaden, 1892, p. 189; Arch. f. exp. Path. u. Pharm., 1893, xxxi, 118.

[3] Arch. f. d. ges. Phys., 1907, cxviii, 268.

in the skin. After such a graft had been made the removal of the intra-abdominal remains of the pancreas did not produce persistent glycosuria. Usually the urine contained sugar for twenty-four hours or less after the operation. Subsequent extirpation of the graft by the simple extraperitoneal operation of removing the graft, without injury to any other structures, produced a severe and rapidly fatal diabetes. Minkowski's experiments were soon repeated and the results confirmed by Hédon[1] and Thiroloix.[2] This experiment has formed one of the chief supports for the theory that the pancreas produces an internal secretion. It led Thiroloix to abandon his theory that the diabetes that followed extirpation of the pancreas was due to gross traumatic lesions of the nerves or nervous plexuses in the neighborhood and to adopt the theory of an internal secretion.

Pflüger[3] insisted that the graft experiment did not overthrow the neurogenic hypothesis. He pointed out that the nerve supply of the portion of the pancreas that formed the graft was unchanged, as the nerves that accompanied the vessels in the mesenteric stalk remained intact and held the graft in connection with the nerve centres.

When Minkowski cut this stalk diabetes resulted, although the graft was left *in situ*. Pflüger explained that this might be due to severing of the nerves rather than to interference with the blood supply. "If centripetal nerves passing from the pancreas can inhibit the activity of the sugar centres of the brain and spinal cord, then the section of these inhibitory nerves would result in an increased production of sugar" (Pflüger[4]).

Hédon[5] in 1892 reported one experiment in which the vascular stalk of the graft was tied without diabetes resulting. This was done on July 6. During the following two days 800 c.c. of urine were passed containing 4 per cent. of sugar. The glycosuria then disappeared. On July 15 the graft was extirpated. Severe diabetes followed. In 1898, Hédon[6] was able to report only

[1] Comp. rend. Soc. de biolog., 1892, iv, pp. 307, 678.
[2] Bull. de la Soc. anatom., 1892, lxvii, 483.
[3] Das Glycogen, Bonn, Zweite Auflage, 1905, p. 504.
[4] Das Glycogen, p. 504.
[5] Arch. de Physiol., 1892, xxiv, 617.
[6] Travaux de Physiologie, 1898. Quoted by Hédon in Revue de médecine, 1910, xxx, 622.

two additional experiments out of a large series in which he tied the pedicle without diabetes resulting.

The following abstracts of these two successful experiments are given by Pflüger.[1] I have not had access to the original publication of Hédon.

Experiment 19. Subcutaneous transplantation March 1. After eighteen days total extirpation of the intra-abdominal pancreas and ligature of the mesenteric pedicle of the graft. Transitory glycosuria. After three days the urine was free from sugar. Graft extirpated March 23. Severe diabetes.

Experiment 20. Subcutaneous transplantation March 24. After nineteen days, on April 12, total extirpation of the intra-abdominal remains of the pancreas and resection of the mesenteric stalk between two ligatures.

From April 13 to 17 only traces of sugar in the urine.

April 17. Extirpation of the graft. Diabetes.

In a single experiment made in Minkowski's laboratory Lombroso[2] cut the vascular stalk of a subcutaneous graft without the production of diabetes. This was done one month after the graft was placed under the skin. During this period there were traces of sugar (less than 0.3 per cent.) in the urine. For four days after the operation there was definite glycosuria which at first amounted to 1.5 per cent., but steadily decreased. Twelve days after tying the stalk the graft was excised. Severe diabetes developed and continued until the death of the animal. The success of the experiment was undoubtedly due to a new-formed artery which was found growing into the graft from the skin. This nourished the pancreatic tissue after the original blood supply was shut off.

Martina an assistant of Payr made an experiment that has been widely quoted. A detailed report of the work was not published owing to the death of this young investigator. The only description that exists is in the report of a meeting of the Medizinischer Verein in Greifswald. Martina[3] in discussing a paper by Minkowski stated that on January 18, 1906, he removed half of the pancreas

[1] Loc. cit.

[2] Boll. Associazione Cultori Scienze mediche e naturali, Rome, 1908. Abstracted in Ergebnisse der Physiologie, 1910, ix, 11.

[3] Deutsch. med. Wochenschrift, 1908, p. 45.

from a dog and transplanted it in the spleen using the method that Payr had devised for transplanting the thyroid. The piece of pancreas measured 18 cm. in length. The operation was followed by no symptoms. On March 14 the remaining half of the pancreas was extirpated. Sugar appeared in the urine on the second day after the operation. It varied in amount from 3 to 6 per cent.; occasionally it ran as high as 9 per cent. The animal died on July 15 of suppurative peritonitis, which took its origin from a fistula in the abdominal wall. At the autopsy no pancreatic remains were found at the site of the pancreas. The portion of the organ transplanted in the spleen was "*volkommen eingeheilt.*" It showed central necroses, but the peripheral cells in contact with the splenic tissue were found on microscopic examination to be intact. As the transplant was entirely separated from the nerve supply of the pancreas Minkowski regarded this experiment as furnishing strong evidence against the neurogenic theory. It should be pointed out that the graft did not prevent the development of glycosuria. In fact, the animal had a severe diabetes. It lived the unusually long period of four months after the extirpation of the pancreas, and this would indicate that the pancreatic tissue in the transplant was functionating, provided there was no pancreatic tissue left *in situ* when the gland was removed.

Attempts have been made to transplant bits of pancreas into the spleen by Alessandri,[1] Ottolenghi,[2] and Tiberti.[3] These investigators used guinea-pigs. They concerned themselves with the degenerative changes in the pancreatic cells and brought forward no evidence to indicate that the pancreatic grafts were able to live and functionate.

Payr's[4] studies showed that transplanted bits of tissue were specially well nourished in the pulp of the spleen. We sought to study the influence of pancreatic transplants in the spleen in the prevention of diabetes. Direct implantations were made except in one experiment, when a graft was supplied with a vascular

[1] Policlinico, 1896, p. 253; 1897, p. 289. Cited by Ottolenghi.

[2] Arch. italien. de biol., 1901, xxxvi, 447.

[3] Sperimentale, 1908, lxii, 389. Cited by Lombroso in Ergebnisse der Physiologie, 1910, vol. ix, 57; Arch. ital. de biol., 1909, li, p. 123.

[4] Arch. f. klin. Chir., 1906, lxxx, 730; Verhandl. d. deutsch. Ges. f. Chir., 1908, vii, 31.

stalk. Such an investigation promised to yield information which would either support or oppose the theory of an internal secretion. If diabetes did not occur it was planned to determine the limit of tolerance for carbohydrates and to keep the animals under observation for a long period. A histologic examination of the grafts was undertaken with the hope of obtaining new knowledge on the relation of the islands of Langerhans to the internal function of the pancreas.

Minkowski and Hédon had shown that subcutaneous grafts would prevent for a short time the occurrence of diabetes. It was not known whether a graft would carry on the internal function of the pancreas for several months or longer.

In the experiments with subcutaneous grafts provision had been made by investigators for the discharge of the external secretion. In three of Minkowski's dogs the pancreatic fistula in the skin failed to develop. In these animals atrophy of the graft was followed by diabetes in thirty-seven days or less. The following abstracts are from Minkowski's protocols:

EXPERIMENT 17. Graft 8 cm. long placed under skin on June 24. The graft swelled at first, later became small and hard. Extirpation of intra-abdominal pancreas July 15. Glycosuria developed July 22.

EXPERIMENT 18. Subcutaneous graft 5 cm. long, February 17. Extirpation of pancreas March 7. Diabetes followed. Death March 14. No trace of graft found.

EXPERIMENT 19. Subcutaneous graft 3.5 cm. long, March 3. After two weeks graft so small as to be scarcely palpable. Pancreatectomy April 6. Diabetes developed April 9.

Judging from this experience and that reported by Sandmeyer,[1] in his study of the effect of partial extirpation of the pancreas, one would expect that a graft in the spleen, where no escape for external secretion were possible, would be followed by atrophy of the graft and diabetes. Our previous observations[2] had shown, however, that extreme atrophy of the pancreas and complete occlusion of all the pancreatic ducts can occur without diabetes supervening.

[1] Zeit. f. Biol., 1892, vol. xxix, p. 112, 1894, xxxi, 12.

[2] Pratt, Lamson, and Marks, TRANS. OF THE ASSOC. OF AMER. PHYS., 1909, xxiv, 266. Pratt and Spooner, Arch. of Int. Med., 1911, vii, 665.

One dog lived thirty-four months after permanent occlusion of all the pancreatic ducts.[1]

In the present study dogs and cats were used. Tissues were fixed in Zenker's fluid or 10 per cent. formalin, imbedded in paraffin and stained with eosin and methylene blue.

DIRECT IMPLANTATION OF PANCREATIC TISSUE IN THE SPLEEN

EXPERIMENT 1. Female dog, weight 5300 grams. Operation November 8. Animal has not been fed for twenty-four hours. Ether narcosis. Incision in median line of abdomen. A tight ligature was placed about the processus uncinatus and a transverse section made just distal to the point of constriction. The terminal portion of the processus uncinatus about 5 cm. long, 2 cm. wide, and 2 to 3 mm. thick was removed after tying the vessels connected with it. An incision 4 cm. long was made in the lower end of the spleen, and with a sharp knife a pocket was made in the substance of the organ. The peritoneal coat of the excised portion of the pancreas was partly removed. The graft was then buried in the spleen. The wound in the spleen was closed with interrupted sutures. The oozing quickly stopped. The hemorrhage produced a tumefaction about 3 cm. in size beneath the surface of the spleen near the incision.

November 9. Urine voided since the operation, 52 c.c. Specific gravity, 1058. No sugar. Urine slightly levorotatory. The dog is lying quietly in the cage. She took 150 c.c. of warm milk this morning.

November 10. On approaching the cage the dog rose to her feet. Given 250 c.c. of milk. Urine, 250 c.c. Specific gravity, 1025. No reduction of Fehling's solution.

November 11. The dog is bright and active.

Symptoms of distemper developed on November 15 and she died on November 27.

Autopsy. Small, fairly well-nourished dog. Pus exudes from a stitch abscess at the site of the operation wound in the skin. Small foci of suppuration in the abdominal wall. None of the abscesses connects with the peritoneal cavity.

The peritoneum is smooth and glistening. The spleen is of normal size and natural appearance externally. Firm adhesions unite the omentum to the spleen. The pancreatic transplant is represented by a mass of rather soft, grayish-white tissue imbedded in the substance of the spleen. It is separated from the splenic substance by a grayish opaque wall 1 mm. thick. The graft is only slightly adherent to the wall, and on section of

[1] Pratt, Jour. of the Amer. Med. Assoc., 1912, lix, 322.

the organ it fell away leaving a small cavity lined by a white membrane. The splenic tissue about the graft appears natural. There are no areas of hemorrhage in the spleen.

Sections through the spleen at the site of the graft show a large area of necrotic tissue surrounded by a zone of pigmented cells. Beyond this is a wall of wide-meshed connective tissue. No pancreatic tissue found.

Experiment 2. Male dog, weight, 5000 grams. November 10. No food for twenty-four hours. Operation under ether narcosis. A portion of the processus uncinatus of the pancreas measuring 5 cm. in length was excised and imbedded in the spleen. After closing the incision in the spleen the omentum was drawn over the wound and sutured to the spleen.

November 12. Rapid recovery from the operation. Urine, 310 c.c. Specific gravity, 1012. Sugar, 0.55 per cent. Amount, 1.7 grams.

November 14. Urine free from sugar. The dog was sent to the dog farm where it died of distemper on December 6.

Autopsy. Dog fairly well nourished. Aside from a small subcutaneous abscess the operation wound is completely healed. Peritoneal cavity dry; serosa, pale and glistening. The omentum is firmly adherent both to the anterior and posterior surface of the spleen. The lower third of the spleen is swollen measuring 1.5 cm. in thickness while the remainder is only half this size. The pancreatic graft is represented by a soft, pale yellow body of almost circular outline and measuring 1 cm. in diameter. On the anterior surface the graft is joined to the omental tissue. The spleen is firm and pale red on section.

Microscopic Examination. The site of the graft is occupied by structureless necrotic material. Between this and the splenic tissue is a zone of granulation tissue containing in its meshes many endothelial cells, some of which contain blood pigment.

Experiment 3. Male dog, weight, 9100 grams. November 29. Operation under ether. Processus uncinatus of pancreas tied off between ligatures. Peritoneal covering partially removed. Pancreatic tissue sliced into strips 6 cm. long, 1 cm. wide, and 0.5 cm. thick. One of these was transplanted into the lower pole of the spleen, and a second piece with peritoneum attached to one side buried in the upper part of the spleen. Incisions in the spleen closed with interrupted fine linen sutures. The opening in the upper pole of the spleen is made longer than usual, making a trough rather than a pocket. Omentum drawn over incisions and stitched in position. In this operation a dull knife was used. Some tearing of the splenic tissue and excessive hemorrhage resulted.

The dog recovered from the operation, but soon was attacked with distemper. He was killed on December 12.

Autopsy. Body warm. Rigor mortis not present. Operation wound healed. The upper end of the spleen adherent to the parietal peritoneum, the lower end to the small intestine and its mesentery. The lower part

of the spleen is not thickened. The graft is represented by a bit of soft white material about 1 cm. long and 1 to 2 mm. thick. Occupying the site of the upper graft is a mass of fairly firm pinkish tissue, 1 cm. in diameter. It is closely adherent to the surrounding splenic substance and reaches the surface of the organ.

Microscopic Examination. Sections through the spleen show that the grafts have been entirely destroyed and converted into necrotic material containing many chromatin fragments and polynuclear leukocytes. Young connective tissue separates the necrotic mass from the splenic tissue.

Experiment 4. Female dog. Operation November 29, under ether. The processus uncinatus tied off between ligatures. A piece of this, 7 cm. long, 1 cm. wide, and 0.5 cm. thick, so cut as to be free from peritoneal covering was planted in the lower lobe of the spleen. A deep pocket was made and the graft fixed in place without tension or pressure. The line of incision covered with omentum.

The dog made a good recovery. As distemper subsequently developed she was chloroformed on December 12.

Autopsy. Body warm. Operation wound healed. Spleen, 10.5 cm. in length; upper part thin and narrow, 2 cm. wide, and 6.5 cm. long; lower part, bulbous, 4.5 cm. wide, and 4 cm. long. On section of this swollen part of the spleen a soft red disintegrated substance exudes. There is a zone of grayish red tissue, 4 mm. thick, surrounding this softened material.

Microscopic Examination. A bit of pancreatic tissue, 1 mm. long, and about 0.1 mm. wide was found. It is composed of acini. No islands of Langerhans present. Near this are a few isolated acini imbedded in connective tissue. Most of the acini take the nuclear stain well. There is no leukocytic or lymphocytic infiltration about the pancreatic cells.

Separated from this graft by a fibrous wall, 1 mm. thick, is a large mass of necrotic tissue. Sections from other parts of pancreatic transplant showed only necrotic material and young connective tissue.

Comment. Thirteen days after transplanting a piece of pancreas into the spleen normal appearing acini were found. But out of a graft measuring 7 x 1 x 0.5 cm. only a tiny nodule 1 x 0.1 mm. remained.

Experiment 5. Male dog, weight, 9400 grams. *First operation,* April 6, under morphine and ether. The processus uncinatus of the pancreas was sectioned between two ligatures at a point 6 cm. from the distal end. Omentum was placed between the divided portions.

Second operation, April 13. The dog was given morphine subcutaneously before etherization. In the anterior abdominal wall in the vicinity of the first incision was a large amount of chronic inflammatory tissue. The

pancreas was of increased consistence and greatly swollen. The terminal portion of the processus uncinatus was closely bound to the remainder of the gland from which it has been separated at the first operation, and the omental tissue which had been placed between the two had almost disappeared. The separation of the two portions was easily made and no connections found except on the external surface of the gland. The isolated part of the processus uncinatus has undergone considerable atrophy. It is of firm consistence and the surface is granular. It measures 3 cm. in length, 2 cm. in width, and 1.5 cm. in thickness. On section, no duct was visible and no hemorrhage or fat necrosis found. An incision was made in the lower part of the spleen and several thin transverse sections of the atrophied pancreas were placed in a deep pocket which was prepared in the usual manner. A few grafts were also buried in the upper end of the spleen. The two incisions in the spleen were closed with silk and were left uncovered by omentum. On attempting to separate the corpus pancreatis from the duodenum the serosa and a portion of the muscular coat were torn away from the wall of the duodenum which was abnormally friable. Owing to the inflamed state of the pancreas the separation of this organ from the gut was abandoned. When seen several hours after the operation the dog was walking about the cage and in good condition.

April 14. At 9.30 A.M. he was found lying on his side and would make no attempt to rise. He died half an hour later (eighteen hours after the operation).

Autopsy. The serosa of the small intestines is dull and lusterless and covered with elevated lines and nodosities, which are apparently produced by irregular contractions of the muscular coat of the intestine. There are about 50 c.c. of bloody fluid free in the peritoneal cavity and considerable hemorrhage about the wound in the abdominal wall and in the mesentery near the pancreas and duodenum. The pancreas is swollen, the surface smooth, and the consistence firmer than normal. The gland surrounds one-half of the duodenum. There are no foci of hemorrhage or fat necrosis. The duodenum is of normal color and its wall is not apparently inflamed. The spleen is slightly larger than at the time of operation. Scattered over its plum-colored surface are a number of darker nodular elevations averaging 1 cm. in size. These mark the direction of the burrows made in the spleen and on section are found to be composed of blood. The two incisions in the spleen are closed by sutures and there is no evidence of any escape of blood from them. The grafts of pancreas placed in the spleen yesterday have disappeared. In their place are a few small shreds apparently of clotted blood. The splenic pulp surrounding the pockets appears normal. Heart, lungs, liver, and kidneys normal.

Microscopic Examination. Spleen. The pancreatic transplants have been converted into structureless necrotic material containing fragmented

nuclei and hemorrhagic areas; no infiltration with polynuclear leukocytes. Between the necrotic material and the splenic tissue are here and there scanty remains of pancreatic tissue. One of these measures 2 mm. in length. The acini in some places stain well and are of normal appearance. In other sections the acini are so distorted that they resemble giant cells.

Experiment 6. A strongly built, well-nourished female dog, weight 8800 grams. Operation, April 13, under ether. A burrow was made with scissors in both the upper and lower ends of the spleen and four or five thin transverse sections of the partially atrophied pancreas of the dog used in Experiment 5, which had been removed thirty minutes previously, and kept in moist gauze, were inserted into the lower pocket in the spleen and three or four sections into the upper pocket.

The pancreas was separated from the duodenum. Two goodly sized ducts were found and tied. In making the dissection a large branch of the pancreatico-duodenal artery was cut. The omentum was drawn between the pancreas and the duodenum.

April 14. This forenoon the dog was walking about her cage and did not seem sick. When seen at 12 o'clock she was apparently in good condition. At 2 p.m. she was found dead and rigor mortis was already present (death twenty-one hours after the operation).

Autopsy. No evidence of infection about the fresh abdominal wound. Peritoneal cavity dry and the serosa smooth and glistening. The stomach is moderately distended. There are some petechiæ on its serous coat. The pancreas is not swollen and is of lax consistence. There are no hemorrhages into the pancreas, and no fat necrosis. The ducts are not dilated. The spleen is swollen. It measures 13 x 5 x 1.5 cm. Several hemorrhagic areas have produced nodular elevations of the surface. The organ was carefully sectioned, but not a single pancreatic graft of those placed in the spleen the day previous to the dog's death could be found. The channels in the spleen made at the operation contain only dark red, soft homogenous material apparently blood and splenic pulp. The heart is distended with blood. The lungs are pale and flaccid. The liver is of normal size and appearance; no focal necroses seen. Kidneys are normal.

Microscopic Examination. On section of the spleen not a trace of pancreatic tissue can be found. Pancreas. There is degeneration of the acini and a few small areas of fat necrosis.

Comment. The results in the last two experiments are remarkable. While the grafts of normal pancreas used in the other dogs did not produce any symptoms, the two dogs which had grafts from a pancreas the seat of a mild acute pancreatitis died within twenty-four hours. The dog (Experiment 5) which had acute pancreatitis as revealed by the operation seemed perfectly well

prior to the implantation of the pancreatic tissue in the spleen. Yet the transfer of a bit of its own pancreas to the spleen caused speedier death than in the case of the normal dog. This dog (Experiment 6) seemed well until less than two hours before its death. Toxins such as the diphtheria toxin act in this way. A rabbit injected with a lethal dose of diphtheria toxin may not appear sick until less than an hour before death occurs. The implantation of a normal pancreas in the peritoneum causes the death of the animal, but v. Bergmann and Guleke[1] found that a preliminary injection of trypsin conferred immunity. On the other hand, our dog, the subject of mild inflammation of the pancreas appeared very susceptible to the toxic action of the pancreatic grafts, more so in fact, than the normal dog. This is a subject that is worthy of further investigation for it promises to throw new light on the toxic action of the pancreas and the cause of death in acute pancreatitis.

Experiment 7. Male dog, weight 8 kilos.

January 12. Fed meat, 300 grams; **glucose,** 115 grams.

January 21. Urine, 80 c.c.; acid, specific gravity, 1036. No sugar.

February 11. Fed meat, 300 grams; **glucose,** 125 grams.

February 12. Urine, 175 c.c.; specific gravity, 1050. Sugar, 0.3 per cent. Amount, 0.53 grams.

February 16. Weight, 7600 grams. *First operation,* ether narcosis. Pancreas large and of normal appearance. Corpus pancreatis, 7 x 2.5 cm.; processus uncinatus, 10 x 2.5 cm.; processus lienalis, 10 x 2.5 cm. A large pancreatic duct was found on the ventral surface of the corpus pancreatis, midway between the upper and lower boundary of this portion of the pancreas. It was directly behind a branch of the pancreatico-duodenal vein. About 3 cm. above this was a second duct nearly as large. Both were cut between double silk ligatures and the intestinal ends buried in the wall of the duodenum. The pancreas was separated from the duodenum and omentum placed between the two. A portion of the processus uncinatus measuring 7 cm. in length and 2 to 3 cm. in width, was removed by cutting between double ligatures. This was cut into thin longitudinal strips with the blade of a safety razor. Some of these pieces were placed in a pocket made by separating the peritoneum from the upper part of the right rectus muscle near the operation wound. A large deep incision was made in the spleen. A piece of gauze was placed in this wound and

[1] Münchener med. Wochenschrift, 1910, No. 32.

time allowed to permit clotting of the blood. A sheet of pancreatic tissue, 3 cm. long, 1 cm. wide, and 1 to 2 mm. thick, was pushed into the pocket. There was still some oozing of blood when the grafts were buried in the spleen. The incision in the spleen was closed with sutures and covered with omentum.

Recovery from the operation was rapid.

March 1. Weight, 6400 grams.

March 6. Fed meat, 300 grams; **glucose,** 100 grams.

March 7. Urine, 400 c.c.; specific gravity, 1020. No reduction of Fehling's solution. The dog has a ravenous appetite, but seems weak. The stools have been numerous and of large caliber. They contain a great number of muscle fibers.

March 8. Weight, 5800 grams. He is now unable to jump into his cage. Fed meat, 300 grams, and **glucose,** 125 grams.

March 9. At 11 A.M. no urine voided since yesterday.

March 10. Three hundred and thirty c.c. of urine beneath cage; specific gravity, 1033. No sugar. Fed meat, 300 grams; **glucose,** 125 grams.

March 11. Urine, 345 c.c. Specific gravity, 1035; slight trace of albumin. Sugar, 0.2 per cent.; amount, 0.64 grams.

Fed meat, 500 grams; **glucose,** 100 grams.

March 12. Urine, 265 c.c.; no sugar.

March 13. Weight, 6000 grams.

March 20. Weight, 5900 grams. Fed meat, 500 grams, and **glucose,** 100 grams. Five hours later 100 c.c. of urine were collected. This contained 4.8 per cent. of sugar.

March 21. Urine voided since yesterday afternoon is free from sugar.

On April 26, the feeding of raw pancreas was begun and continued until May 19.

May 5. Fed meat, 300 grams; 3 pancreas; **glucose,** 100 grams.

May 6. Urine, 140 c.c.; sugar, 0.6 per cent.

May 23. Weight, 5900 grams.

August 18. Weight, 5200 grams. Fed meat, 300 grams; **glucose,** 100 grams.

August 19. Urine, 370 c.c.; sugar, 3.75 per cent.; amount, 13.87 grams.

August 22. Fed meat, 300 grams; **glucose,** 50 grams.

August 23. Urine, 180 c.c.; specific gravity, 1035. A trace of sugar present (slight reduction of Fehling's solution on standing).

August 24. Fed meat, 300 grams; **glucose,** 45 grams.

August 25. Urine, 145 c.c.; specific gravity, 1035. No sugar.

Second operation, September 11. Morphine-ether anesthesia. Omentum, liver, and upper part of small intestine including duodenum bound together by adhesions. After separating adhesions the duodenum was brought outside the abdomen and the region of the pancreas exposed. The pancreas was represented by a small, dense mass attached to the wall of the

duodenum, 2 to 3 cm. below the pylorus, grayish white on section, and apparently composed of scar tissue. Its outlines were indistinct as it merged into the adhesions about the omentum, intestine, and retroperitoneal tissues. Attempts to remove it were abandoned after cutting a large branch of the pancreatico-duodenal artery. The spleen was removed.

September 12. Weight, 4700 grams. The dog is lively and drinks water freely. At 11 A.M., amount of urine voided since the operation yesterday (eighteen hours), 85 c.c. It was free from sugar; specific gravity, 1023.

September 18. Weight, 4600 grams. Dog is weak. Fed meat, 300 grams; **glucose,** 40 grams. Vomited a few minutes later.

September 20. Fed meat, 300 grams; **glucose,** 30 grams. He did not eat all of this mixture.

September 21. Urine, 70 c.c. It reduces Fehling's solution; 0.2 per cent. sugar. Dog ate very little of the 300 grams of meat, and 300 c.c. of milk given today.

September 22. Found dead in cage this morning.

Autopsy. Body of a greatly emaciated dog, weight, 4100 grams. Operation wound, not fully healed; some thin pus exudes. The anterior abdominal wall is thickened in the region of the incision, measuring, 1 to 2 cm. in thickness. It consists of a grayish-white tissue, probably necrotic. It has a worm-eaten appearance due to communicating areas of softening. The inflammation extends through the entire abdominal wall. The edge of the liver, pyloric end of stomach, and the duodenum, are firmly adherent to the abdominal wall. The serosa of this portion of the peritoneal cavity is injected and in places covered with shreds of fibrin. The pancreas is represented by a nodule measuring 2 cm. in length, and 1 cm. from above downward. On section, it is firm and grayish white with lax texture as if composed of connective tissue. Scattered through it are yellowish opaque areas about 1 to 2 mm. in size.

Microscopic examination of tissues removed at operation and at autopsy. Serial sections of the spleen through the site of the graft revealed no pancreatic tissue. Many sections of portions of the anterior abdominal wall were examined, but they showed no remains of the pancreatic graft.

COMMENT. On August 25 the dog was able to take 45 grams of glucose without the production of glycosuria. The spleen was removed on September 11. On September 20, sugar appeared in the urine when less than 30 grams of glucose were taken. This reduction of tolerance may have been produced in various ways. It was due possibly to the presence of functionating pancreatic tissue in the spleen, although none was recognized on microscopic examination. It is more probable that the lowered limit of assimi-

lation was the result of injury to the atrophied pancreas during the operation and to interference with its blood supply. Hence, no definite conclusion can be drawn from this experiment in regard to the function of the pancreatic graft. It does, however, confirm in a striking manner the claim of Pratt and Spooner[1] that the occlusion of all the pancreatic ducts produces extreme atrophy of the pancreas and lowered tolerance for glucose.

Experiment 8. Cat, March 8. *Operation* under ether narcosis. The pancreas seemed unusually soft. The processus uncinatus measuring about 5 cm. in length, and 1 cm. in width, was cut into pieces each about 1 cm. long, and 3 to 4 mm. thick. The spleen was long and thin. A pocket 4 to 5 cm. long was made in the lower half of the spleen and in this the pieces of pancreas were placed. There was very little bleeding during this procedure. The incision in the spleen was closed with two silk ligatures. The body of the pancreas was then separated from the duodenum in the usual way.

March 9. The cat lies quietly in the cage and seems sick.

March 10. The cat was found dead this morning.

Autopsy. Serosa, smooth and glistening. The corpus pancreatis and the processus lienalis are firm and edematous. Areas of fat necrosis, 1 to 2 mm. in size, and of yellowish-white color are present on the mesenteric and omental tissue near the pancreas and on the pancreas itself. The duodenum is firm, pale, and swollen. No hemorrhagic areas seen. No inflammation about the spleen. The lower half is twice the thickness and twice the width of the upper half of the organ. An elevated hemorrhagic area extends upward 3 cm. from the incision in the lower part of the spleen. There has been no bleeding into the peritoneal sac. On section of the spleen the pancreatic graft, 5 to 7 mm. wide, was surrounded by splenic tissue with only a thin, dark line of hemorrhage between the two.

Microscopic Examination. Examination of the spleen in the region of the graft shows almost complete disappearance of the pancreatic tissue. What had been mistaken for the graft on the gross examination is necrotic material. This is infiltrated with blood. Surrounding a portion of this hemorrhagic area is a thin rim of pancreatic tissue. In one section a bit of pancreas, 2 x 2 mm. was found. The acini are more or less fused together so that their outline and that of the component cells are indistinct. In places the acinar structure is entirely lost. Nothing seen that can be identified as an island of Langerhans.

[1] Archives of Internal Medicine, 1911, vii, 665.

Experiment 9. Operation, March 13, on a well-nourished male cat. Ether narcosis. Large pancreatic duct entering just below common bile duct was dissected out and cut between double ligatures. A second smaller duct found, 1 cm. below the first duct. It was ligated in a similar manner.

The corpus pancreatis was freed from the duodenum, sparing no connecting vessels that passed between the upper half of the corpus pancreatis and the intestine. Processus lienalis removed. It was 15 cm. long, and 1 cm. wide. A long, narrow pocket was made in the spleen after making an incision 1 cm. long near its lower pole. The lower half of the spleen was burrowed with scissors upward for a distance of about 5 cm. and downward 2 cm. With forceps a strip of pancreas 3 cm. long, and 3 cm. wide was taken from the splenic end of the pancreas and inserted into the upper pocket and a second strip, 1.5 cm. long was pushed into the lower pocket. The opening in the spleen was closed with two linen sutures, and no omentum attached to it.

March 21. Cat found dead this morning. He had not been well since the operation. Yesterday he refused food and appeared weak and listless.

Autopsy. There is serosanguinolent fluid in the subcutaneous tissue in the vicinity of the incision, but no evidence of pyogenic infection. Peritoneal cavity is dry; serosa, smooth. The duodenum and pancreas are bound quite firmly to the omentum and mesentery. The wall of the duodenum is intact. The corpus pancreatis is very firm and considerably swollen. It is separated from the duodenum by thickened omentum. This portion of the pancreas is 1.5 cm. in average width, and 3 to 4 mm. thick. The surrounding fat tissue is firmer than normal. In color and consistence it resembles the pancreatic tissue so closely that the outlines of the pancreas cannot easily be made out. On the mesentery and omentum near the body of the pancreas are a dozen or more areas of fat necrosis, 1 to 3 mm. in size. About the ligated end of the main pancreatic duct the tissues are softened over an area about 5 mm. in size. The spleen is 9 cm. long. The larger pancreatic graft is represented by a firm yellowish-white mass 5 mm. in diameter and about 2 cm. long, lying in close contact with the splenic tissue which is deep red and firm. The lower pocket is filled with a blood clot.

Microscopic Examination. The graft in the spleen is necrotic and structureless except for a thin broken line of pancreatic epithelium between the necrotic mass and the splenic tissue. The epithelial cells occur singly and in small groups which resemble giant cells. No definite acini seen. Other sections through the site of the grafts show hemorrhagic and necrotic areas but no pancreatic cells.

SUMMARY OF PRECEDING EXPERIMENTS

Pancreatic transplants to the spleen undergo rapid antolysis. In six out of nine animals examined eighteen hours to two hundred and eighteen days after the transplantation, no pancreatic tissue was found. In one experiment well-preserved acini were found thirteen days after the transplantation.

Experiment 1. Dog; nineteen days after transplantation no pancreatic cells found in spleen.

Experiment 2. Dog; twenty-six days after transplantation to spleen no pancreatic cells found.

Experiment 3. Dog; thirteen days after transplantation to spleen no pancreatic cells found.

Experiment 4. Dog; thirteen days after transplantation to spleen a bit of pancreatic tissue 1 mm. x 0.1 mm. in size found. It consists of acini surrounded by connective tissue. No islands of Langerhans.

Experiment 5. Dog; eighteen hours after transplantation to spleen of pancreatic tissue the seat of mild inflammation (autoplastic transplant). Only scanty remains of pancreatic tissue found.

Experiment 6. Dog; twenty-one hours after transplantation to spleen of pancreatic tissue the seat of mild inflammation (homoplastic transplant). No pancreatic cells found.

Experiment 7. Dog; two hundred and eighteen days after transplantation of pancreatic tissue to spleen. No pancreatic remains.

Experiment 8. Cat; two days after transplantation to spleen. A thin zone of pancreatic tissue. It is composed of acini.

Experiment 9. Cat; eight days after transplantation to spleen. Thin layer of pancreatic cells between spleen and necrotic material.

PANCREATIC TRANSPLANT IN SPLEEN WITH BLOOD SUPPLY TEMPORARILY PRESERVED BY MEANS OF A MESENTERIC STALK

Experiment 10. Male dog, weight, 13 kilos.

January 16. Fed meat, 300 grams; **glucose,** 100 grams.

January 17. Urine, 250 c.c.; specific gravity, 1026. No sugar.

January 20. Fed meat, 300 grams; **glucose,** 115 grams.

January 21. Urine, 230 c.c.; specific gravity, 1030. No sugar.

February 10. Fed meat, 300 grams; **glucose,** 125 grams.

February 11. Urine, 185 c.c.; specific gravity, 1052; sugar, 0.3 per cent.; amount, 0.49 grams.

February 13. *First operation*, weight, 11,100 grams. Morphine given subcutaneously prior to operation. The processus uncinatus was separated from the remainder of the pancreas at a point 5 cm. from the end by cutting between double ligatures. An incision was made in the mesial surface of the spleen and a large pocket prepared. Into this was introduced a large pancreatic graft which measured 5 cm. x 3 cm. During this manipulation a considerable amount of blood was lost. Finally, all the pancreatic tissue, except about 1 cm. of the terminal portion, was within the spleen. The mesenteric stalk attached to the end of the processus uncinatus which contained an artery and vein, both of goodly size, was preserved. The graft was secured in place by sutures and the omentum was drawn around the vascular pedicle.

The dog made a good recovery.

March 7. *Second operation*, weight, 9100 grams. Morphine-ether anesthesia. On opening the abdomen a large mass was found behind the coils of intestine covered with mesentery. This was an abscess occupying the lower part of the spleen. It was opened and found to contain about 30 c.c. of thin pinkish puriform material which had a pleasant odor resembling that of heliotrope. A portion of the pancreatic graft about 2 cm. in size projected from the spleen. Its outline could not clearly be made out as it was nearly surrounded by mesentery. The stalk supplying the graft was torn and the vessels tied. There was no inflammation of the pancreas or duodenum. The stump of the processus uncinatus was healed and free from adhesions to surrounding structures. The duodenum was stripped clean of pancreatic tissue. Two ducts were found and cut between double ligatures. The pancreatico-duodenal artery and vein were spared. The whole pancreas was removed. The extirpated pancreatic tissue weighed 19 grams.

March 8. The dog is active. Water given in the afternoon. At 10 A.M. 110 c.c. of urine under cage; specific gravity, 1046. It does not reduce Fehling's solution.

March 9. Urine, 150 c.c.; no sugar.

March 10. Urine, 305 c.c.; no sugar. Fed meat, 300 grams; milk, 300 c.c.

March 11. No sugar in urine. Fed meat, 400 grams; **glucose,** 75 grams.

March 12. Urine, 160 c.c.; sugar, 1 per cent.; amount, 2.08 grams.

March 13. Urine, 240 c.c.; specific gravity, 1055; no sugar. Fed meat, 500 grams; **glucose,** 50 grams.

March 14. Urine, 230 c.c.; specific gravity, 1050; sugar, 0.6 per cent.; amount, 1.38 grams. Fed meat, 500 grams; milk, 300 c.c.

March 15. Weight, 7900 grams. Urine, 410 c.c.; specific gravity, 1035. No reduction of copper. Fed meat, 500 grams; **glucose,** 30 grams.

March 16. Urine, 220 c.c.; specific gravity, 1050; no sugar. Fed meat, 300 grams; **glucose,** 60 grams.

March 17. Urine, 190 c.c.; specific gravity, 1054; sugar, 0.5 per cent.; amount, 0.95 grams.

March 20. Weight, 8125 grams.

March 23. Weight, 7730 grams. Three days absorption experiment ended today. Dog is weak, but does not seem sick.

March 25. At 11 A.M. dog ate meat, 500 grams, and milk, 300 c.c. At 12.30 P.M. found lying in cage; unable to stand when placed on his feet. Ate three pancreas greedily (none fed previously to this dog). At 5 P.M. 80 c.c. of urine collected. It is free from albumin and sugar. When taken out of cage the dog lay sprawling on the floor unable to walk or crawl. Given three more pancreas.

March 26. When seen this morning he was standing up in the cage. Fed three pancreas, 500 grams meat, 300 c.c. milk.

March 27. Weight, 7500 grams. Fed meat, 300 grams; three pancreas; **glucose,** 30 grams.

March 28. Urine, 95 c.c.; specific gravity, 1056; sugar, 0.15 per cent.; amount, 0.14 grams. Fed meat, 300 grams; three pancreas; **glucose,** 25 grams.

March 29. Urine, 150 c.c.; specific gravity, 1050; no sugar.

March 31. Weight, 7600 grams.

April 4. Weight, 7150 grams. Fed meat, 300 grams; three pancreas; **glucose,** 100 grams.

April 5. Urine, 225 c.c.; specific gravity, 1070; sugar, 6.2 per cent.; amount, 13.95 grams.

April 10. Weight, 7400 grams. The stools are fewer in number and less bulky. The dog has been fed three pancreas daily. He is now stronger and can jump out from his cage and alight on his feet. Fed meat, 300 grams; three pancreas; **glucose,** 40 grams.

April 11. Urine, 65 c.c.; specific gravity, 1053. No reduction of Fehling's solution.

April 12. Fed at 10 A.M. meat, 300 grams; three pancreas; **glucose,** 50 grams. At 4.45 P.M. 110 c.c. of urine had been voided; specific gravity, 1046; 3.1 per cent. sugar; amount, 3.41 grams.

April 14. Weight, 7900 grams. Fed meat, 300 grams; three pancreas; **glucose,** 100 grams.

April 15. Urine, 210 c.c.; specific gravity, 1062; sugar, 2.8 per cent.; amount, 5.88 grams.

May 1. Weight, 7600 grams. He vomits almost daily. Beginning today he will receive six pancreas daily.

May 24. Fed meat, 300 grams; bone ash, 50 grams; **glucose,** 30 grams.

May 27. Urine, 200 c.c.; specific gravity, 1039; sugar, 1.2 per cent.; amount, 2.4 grams; 200 c.c. more of urine were collected at 6 P.M. This was free from sugar.

June 2. Weight, 7300 grams.

August 17. Weight, 6900 grams. He seems fairly strong. During the last two months and a half he has been given pancreas almost daily. Fed meat, 300 grams; five pancreas; **glucose,** 50 grams.

August 18. Urine, 260 c.c.; specific gravity, 1034; sugar, 3.5 per cent.; amount, 9.1 grams.

August 19. Fed meat, 300 grams; five pancreas; **glucose,** 30 grams.

August 20. Urine, 190 c.c.; specific gravity, 1036; sugar, 0.85 per cent.; amount, 1.61 grams.

August 20. Fed meat, 300 grams; five pancreas; milk, 300 c.c.

August 21. Urine, 400 c.c.; specific gravity, 1040; sugar, 0.85 per cent.; amount, 3.4 grams.

August 21. Fed meat, 300 grams; five pancreas.

August 22. Urine, 360 c.c.; specific gravity, 1035; no sugar.

August 22. Meat, 300 grams; five pancreas; **glucose,** 15 grams.

August 23. Urine, 300 c.c.; specific gravity, 1035; no sugar.

August 24. Fed meat, 300 grams; five pancreas; **glucose,** 25 grams.

August 25. Urine, 145 c.c.; specific gravity, 1050; sugar, 2.5 per cent.; amount, 3.62 grams.

August 25. Fed meat, 300 grams; five pancreas.

August 26. Urine, 360 c.c.; no sugar.

September 10. Dog found lying in cage. He had been ill for five days and had vomited much of his food. Today he was quite powerless, in fact, unable to lift his head. He was chloroformed.

Autopsy. Body of greatly emaciated dog. Weight, 5710 grams. The omentum is free from fat. The retroperitoneal tissues are stained black (old hemorrhage). In the median line of the peritoneal cavity there is an egg-shaped mass, 4.5 cm. x 3.5 cm. This proved to be an abscess cavity which occupies the lower portion of the spleen. A cone-shaped projection of firm grayish-white tissue with its base formed by the wall of the abscess extends into the spleen for a distance of 2 cm. Its maximum diameter is 0.1 cm. This nodule must receive its blood supply from the splenic tissue or the thick fibrous wall of the abscess. The abscess cavity does not connect with the intestine although it is adherent anteriorly to the jejunum and posteriorly to the large intestine. No pancreatic remains found at the site of the pancreas.

Microscopic Examination. The cone-shaped mass extending from the abscess into the spleen was found to consist of dense fibrous tissue. In the centre of this are the remains of the transplant of pancreatic tissue. Imbedded in this tissue are acini scattered over an area about 5 mm. in width and less than 1 cm. in length. Except in a few places where the acini are in close contact they are separated by connective tissue rich in cells. Some of the acini are well preserved and contain a definite lumen. The nuclei are vesicular and situated in the periphery of the cells. The protoplasm is fairly abundant and many of the cells granular. Some

vaculoes are seen. Sections stained with phosphotungstic hematoxylin show blue staining granules in some of the acini cells (zymogen granules). In a few places small, irregular masses of epithelial cells are seen which look like fused acini. Scattered throughout the connective tissue surrounding the pancreatic remains are nerve fibers and occasional ganglion cells. There is no necrotic tissue and no infiltration with polynuclear leukocytes in the vicinity of the pancreatic graft. Between the splenic tissue and the remains of the pancreatic graft is a wall of dense fibrous tissue 2 to 3 mm. thick. The largest amount of pancreatic tissue found in any one section measured about 4 x 2 mm. No islands of Langerhans were found in any part of the graft.

Comment. This dog lived one hundred and eighty-seven days with the internal function of the pancreas maintained by a graft in the spleen entirely separated from its original vascular supply and nervous connections. Although the tolerance for carbohydrates sank to a low point persistent glycosuria did not develop. Inanition due to the absence of pancreatic secretion from the intestine was the cause of death. The feeding of fresh pancreas supplied this lack in part and apparently prevented the death of the animal in the third week following pancreatectomy. The limit of tolerance to glucose rose for a short time after the feeding of pancreas was begun, but was at a fairly constant low level from May 24 to August 20. The pancreatic remains at death as determined by serial sections were less than 1 cm. in size. The larger part of this small nodule was composed of fibrous tissue. Acini were found, and some of the cells contained well-preserved granules staining blue with phosphotungstic hematoxylin and identical in appearance with the zymogen granules of the normal pancreas. As these granules do not occur in the cells of the islands of Langerhans their presence furnishes additional evidence that the pancreatic cells in which they occurred in the graft were acinar cells. No islands of Langerhans were found in any of the sections. If Ribbert's statement is true that only cells that can functionate will live when transplanted, then the presence of normal appearing acinar epithelium in this graft two hundred and nine days after the pancreatic tissue was transplanted into the spleen is evidence that the acinar cells can carry on the internal function of the pancreas. This experiment does not disprove the neurogenic theory

of diabetes, but it presents additional evidence against it, and in favor of the theory of an internal secretion. Furthermore, this experiment overthrows Lombroso's[1] claim that the internal function of the pancreas plays an important part in the absorption of food from the intestine, and confirms the work of Pratt, Lamson, and Marks[2] who found that exclusion of all the external secretion of the pancreas from the intestine produced a great decrease in the absorption of fats and proteins.

This demonstration of the prevention of diabetes for more than six months by means of a small nodule of sclerosed pancreatic tissue in the spleen makes the accuracy of Martina's observations improbable. If his graft in the spleen had remained active, why did sugar appear in the urine two days after the remainder of the pancreas was removed and persist in large amount (3 to 6 per cent.) until the death of the animal? Inasmuch as the animal lived four months with this degree of glycosuria it is probable that some pancreatic juice was entering the intestine, secreted from remains of pancreatic tissue so small that they were overlooked at the autopsy. Among the dogs in which we have shut out all the pancreatic secretion from the intestine marked disturbance of absorption attended with great loss of weight, as shown in this experiment, has always occurred.[3] The fact that Minkowski's dogs with pancreatic subcutaneous grafts did not lose weight after the intra-abdominal pancreatic tissue was removed is conclusive evidence that even this skilful operator left some secreting tissue attached to the intestine.[4]

The weights of the dogs before and after extirpation of the pancreas in Minkowski's experiments were as follows:

EXPERIMENT 14. Weight of dog, 15 kilos.
October 9. Subcutaneous graft.
October 29. Extirpation of intra-abdominal remains of pancreas.
November 24. Weight, 15.5 kilos.

[1] Arch. f. exp. Path. u. Pharm., 1908, lviii, 251.
[2] TRANS. OF THE ASSOC. OF AMER. PHYS., 1909, xxiv, 266.
[3] See the papers by Pratt, Lamson, and Marks, and Pratt and Spooner.
[4] See Minkowski, Arch. exp. Path. u. Pharm., 1893, xxxi, 118.

EXPERIMENT 15. Weight of dog, 9.6 kilos.
November 13. Subcutaneous graft.
November 23. Expiration of intra-abdominal remains of pancreas.
November 30. Weight, 10.2 kilos.
EXPERIMENT 16. Weight of dog, 17 kilos.
May 4. Subcutaneous graft.
June 20. Extirpation of pancreas.
July 19. Weight, 17.2 kilos.

CONCLUSIONS

Pancreatic tissue implanted in the spleen and separated from its original vascular and nervous connections can live and functionate for months. A small nodule of pancreatic tissue composed of acini without demonstrable islands of Langerhans prevented the development of diabetes for a period of one hundred and eighty-seven days after extirpation of the pancreas.

THE EFFICIENCY AND SIGNIFICANCE OF DIFFERENT FORMS OF RESPIRATION

By DAVID L. EDSALL, M.D.
BOSTON

I WISH to describe some experiments with Benedict's new respiration apparatus that I undertook to determine if possible the relative results accomplished by some of the different types of breathing so commonly seen in disease. With myself and others as subjects breathing first normally, then superficially, then as slowly and deeply as possible without distinct discomfort, I determined the CO_2 output, the oxygen intake, and the total ventilation, in fifteen-minute periods, and made (as can be done with this apparatus) quantitative measurements, from the tracings taken concidently, of the ventilation value of each of the individual respirations. In each experiment the deep and the superficial breathing were kept down to the lowest amount possible without producing distinct respiratory distress, in order to make it as nearly certain as possible that the demand for air was, in each instance, being just met, and at any rate not exceeded. Otherwise I should of course have been entirely unable to tell whether these periods could properly be compared with the normal, as it would have been impossible to have told whether we had not breathed much more than necessary. In the abnormal forms of breathing we avoided as far as possible any use of the accessory muscles of respiration, a point of importance in interpreting the results.

In most instances we had the impression of having breathed less in total amount during the period of superficial breathing than in the other periods. In every instance quite the contrary was true. The record always showed in the neighborhood of 25 per cent. more total (tidal) ventilation in this period than in the normal period and

the lowest amount of air used was always in the slow deep breathing; as much as 25 per cent. less than in the normal period and as much as 40 per cent. less than in the period of superficial breathing. Evidently, then, from the standpoint of gas exchange the slow, deep form of breathing is very economical of effort while the superficial form is extremely wasteful.

It is easy to explain why this is true and at the same time the difference becomes emphasized to a rather astonishing degree if we consider the influence of the "dead space." The dead space means, of course, that space in the chest into which, with each respiration, air enters and passes out again, but comes in contact with no areas in which any considerable amount of diffusion of gas occurs to and from the blood, the space, that is, in the upper part of the respiratory tract. How far down toward the alveoli its limits should be put is not wholly clear, as some diffusion appears to occur through the walls of at least the smaller bronchi. Entrance and exit of air into this space is a waste so far as any direct influence upon gas exchange is concerned, and each respiration must therefore have the dead space counted out from the amount of air apparently taken in if we wish to know how much is really efficient in increasing gas exchange. It becomes apparent immediately that the influence of the dead space is much more important in the rapid superficial forms of respiration than in slow, deep breathing, as a little consideration will show at once. Various figures are given for the size of the average dead space. All are to some degree approximate. Used as an average those most commonly accepted are the figures of Löwy, and made the average capacity about 140 c.c. I have taken these figures as a standard factor in calculating the effect of the dead space. Now suppose, for example, that a man breathing deeply takes in 1800 c.c. of air with each respiration, and breathes only four times a minute. He takes in a total of 7200 c.c. each minute. Counting out 140 c.c. of dead space for each of these four respirations, viz., 560 c.c. all told, we have left 6640 c.c. of real or alveolar ventilation. If this man at another time breathes with a normal rate and amplitude, taking in 450 c.c. of air each time, and breathing 16 times a minute, his total ventilation is the same, 7200 c.c.; but we must take out the

dead space 16 times, viz., 16 x 140, or 2240 c.c., and we have left only 4960 c.c. That is, the deep slow breathing would give in this instance 33 per cent. more real or alveolar ventilation than the more rapid type of breathing, which in this instance, however, is the normal type. The difference would be still more marked with a more superficial type of breathing. If he breathed 32 times a minute, taking in 225 c.c. each time, he would again have 7200 c.c. tidal air, but 4480 c.c. must be deducted now so that only 2720 is alveolar ventilation. As compared with this form of breathing the slow deep form with only four respirations per minute would give 144 per cent. more alveolar ventilation. This helps, it would seem to show why in the panting respiration following active exertion an occasional deep breath is so grateful, and why patients with cardiac and other severe disease so often break a rapid, superficial type of breathing with a deep sigh or gasp. The deep breath does the work of a surprisingly large number of superficial ones, but the deep breathing cannot be kept up continuously, probably because of the greater mechanical strain it causes upon the circulation.

The figures that I obtained in a typical example of the experiments that I am now discussing are shown on page 563. In this instance, then, the superficial form required over ten times the number of respiratory efforts that the slow deep form did, and 2.6 times the number of efforts required by the normal form, but the results in CO_2 output and in the oxygen intake were very close to each other in all instances. There is a slight reduction, in the deep breathing period, in the output of CO_2 and a slighter rise in the oxygen intake in both the superficial and deep breathing periods; but this latter rise was due, I think, entirely to the fact that, as I said, in all these experiments an effort was made to keep the respiration down somewhat, and this together with the effort to maintain a form of breathing to which we were unaccustomed led to extra effort, chiefly to a constant tendency to slight action of the accessory muscles of respiration. That there was slight suppression of the respiration is shown by the records for the CO_2 in the alveolar air. These are slightly higher in both the superficial and the deep form of respiration than in the normal period. But the CO_2 output and the oxygen intake, as well as the figures for the alveolar CO_2, are

so close as to serve as good indications of the fact that the three periods can properly be compared with one another as having accomplished just about the same result.

Breathing.	Respirations.		Ventilation.		Alveolar CO_2. per cent.	CO_2 output.		Oxygen absorbed.	
	Average per min.	Total 15 min.	Average per min. liters	Total 15 min. liters		Average per min. c.c.	Total 15 min. c.c.	Average per min. c.c.	Total 15 min. c.c.
Normal	11.6	174	6.21 .... 4.59*	93.25 24.36† 68.89*	6.43	257	3850	304	4580
Deep	2.7	41	4.76 .... 4.37*	71.51 5.88† 65.63*	6.76	234	3517	320	4800
Superficial	31	465	8.70 .... 4.36*	130.60 65.10† 65.50*	6.81	257	3867	314	4720

* Alveolar ventilation. † Dead space

The most striking fact of all, perhaps, is that the real amount of air that reached the alveoli was almost exactly the same in all instances. Much the same results were obtained in all experiments of this sort that I conducted, the alveolar ventilation being in practically all instances within about 5 per cent. of the same amount in all the periods in each experiment. Evidently in whatever way we breathe, nature requires of us only a definitely essential amount of alveolar ventilation, and if other conditions remain the same this amount is the same but the number of breathing efforts required to accomplish this ventilation varies extremely widely with different forms of breathing. It is often stated, especially by physiologists, that very deep breathing is wasteful of effort. My results show precisely the contrary. This is, however, due to the fact that such statements refer to deep *labored* breathing in which much extra muscular effort is used in each respiration. As I stated earlier I was dealing with deep *unlabored* breathing and purposely excluded any violent effort.

What, then, is the explanation of the occurrence of these different types of breathing? The abnormally deep form of breathing can, upon theoretical grounds, be readily thought of as being due to one of two things: It may be due to a loss of the vagus influence upon respiration, the vagus appearing, from the work of Scott and others, to restrain the depth of respiration within normal bounds or it may be the consequence of simply a dulling of the sensitiveness of the respiratory centre, so that it responds only after long intervals and then meets the accumulated demand by a deep respiration. Neither of these alone seems altogether satisfactory. It is somewhat of an assumption to say that loss of vagus control is responsible, for complete loss of vagus control appears to result not simply in deep but also in labored breathing; and, too, we have in many of these cases no other direct evidence that vagus influence is disturbed. On the other hand, if it were due simply to insensitiveness of the respiratory centre, it is not clear why the breathing should be so regular in amplitude in many instances of this kind, and not tend to assume the Cheyne-Stokes characters. It is not improbable, however, that either of these influences may produce this result at times. They may also work in combination and also other factors may come into play. Furthermore, it may be that other influences than a reduction in CO_2 tension or oxygen tension or in the sensitiveness of the respiratory centre are necessary to lend the Cheyne-Stokes characteristics, for Haldane and Douglas' theory while explaining the periodicity does not give any satisfactory explanation of the crescendo-diminuendo character of Cheyne-Stokes respiration. It would seem, however, that those abnormal forms of breathing that show only slow respiration with decided pauses in expiration or distinct periods of simple apnea and those which exhibit Cheyne-Stokes character may often, if not always, be due to causes that differ simply quantitatively not qualitatively, for forced breathing may be followed by either or both of these abnormal forms of breathing. The readiness with which one form merges into the other after forced breathing, the fact that the one cause may produce either or both forms even in the same person, and that all varieties and all intermediate stages from slight periods of simple apnea to marked Cheyne-Stokes breathing may follow

this same cause are matters of decided clinical interest and significance, and must render us somewhat cautious of laying great stress upon the qualitative differences seen clinically in respiratory arrhythmias until we know more about their actual causes. I have many tracings of respiration taken in other experiments, after forced breathing, that illustrate the variability in the character of the respiratory irregularities following excessive breathing. For instance one shows immediately at the beginning of the rest period following two fifteen-minute periods of forced breathing prolonged apnea. For three and a half minutes there is but one breath of considerable size and a few scarcely large enough to avercome the dead space. In fact, there was during that period less than a liter of alveolar ventilation while the same man had about 4.6 liters alveolar ventilation per minute under circumstances differing only in the absence of preceding forced breathing. After this he took a good-sized double breath and then the respiration became very superficial, for some time gradually increasing in amplitude to about normal for him; but there were few and only slight further periods of apnea, no Cheyne-Stokes, and no other marked irregularities in either rate or amplitude. Another is from the same man under the same circumstances, but from another experiment. It shows continuously very great and erratic irregularity of amplitude and rate but few actual marked pauses, though there is strong tendency to the other features of Cheyne-Stokes. Another is characterized chiefly by very superficial breathing, with marked pauses between breaths, the size of the pauses and of the breaths varying a good deal. Later in the tracing there occur slight periods of crescendo breathing, but separated, not by apnea, as in typical Cheyne-Stokes, but by tachypnea. This was after one of the most severe experiments, but the results in the character of the breathing are less marked than in other experiments. In another there is superficial breathing, with marked apneic pauses, also typical short periods of Cheyne-Stokes and other periods showing the Cheyne-Stokes type of breathing minus the apneic periods. In all these the subject breathed simply as he desired without voluntarily influencing the character of his breathing.

The superficial type of breathing in disease seems to me suscep-

tible of more definite explanation than the slow deep form and comprehension of it would be of much more frequent clinical importance. It occurs chiefly in certain toxemias, infectious or other, and in severe circulatory weakness, aside from those instances in which it is simply neurotic. It appears highly probably that excessive accumulations of CO_2, or of other (chiefly unknown) substances that besides CO_2 are almost certainly active in disease in exciting the respiratory centre, irritate the centre excessively in such conditions and produce increased frequency of respiration. Indeed, the centre in many of these cases, when they are severe, is probably continuously irritated, and hence there is a demand for a new respiratory effort almost constantly. There are also other reasons for the occurrence of this breathing in severe circulatory distress. Such breathing may readily modify favorably for the failing heart the frequency and extent of the well-known suction and compression effects of respiration upon the blood stream in the thorax and abdomen that have been so well described by Tigerstedt. While the actual influence upon these of any particular changes in respiration is rather complex, and it is difficult to postulate definitely whether the influence would be good or bad in particular types of cases, there is one point that seems to me to deserve more direct attention than I have seen definitely given to it. Rapid breathing, in lessening the extent of the changes in pressure in the thorax and abdomen that occur in respiration, certainly reduces, as compared with slower breathing, the extent of the variations in systemic blood pressure that are the normal and inevitable consequence of the usual respiratory changes in intrathoracic and intra-abdominal pressure, and, experimentally, very rapid breathing appears even to wipe out entirely the general blood-pressure changes. It may readily be an important source of relief to the heart, when under severe strain or very incompetent, to be freed of the marked variations in strain that occur with decided changes in blood pressure. Increase in respiratory rate from any cause would, however, if carried far, make respiration itself tend to become inefficient or at least make it do much more work in accomplishing the same result, as my figures indicate, for if there is marked increase in the rate, the amplitude of respiration suffers, and amplitude has more

influence on the end result than has the rate. This may easily establish just the same type of vicious circle as occurs under certain circumstances with the heart. With the latter organ, when the rate increases, the amplitude of the stroke tends to become deficient, and hence when working inefficiently, but rapidly, under strain the heart often tends to race still faster because of its failure to accomplish its function, the failure being due to insufficient amplitude of stroke. In racing it makes an ineffectual, and always increasingly hopeless, attempt to make greater rate take the place of amplitude. We have good reason to consider that respiration also often tends to increase in rate at the expense of amplitude when the centre is severely excited. This is clearly indicated by Hough's recent experiments on the different influences in different normal persons of breathing into an enclosed space in which the CO_2 constantly accumulates. In most of his experiments after a time—sometimes very early—the rate increased and usually at the increasing expense of amplitude. Besides the effect of overstimulation of the respiratory centre the rate is, in all probability, hastened to an unduly great extent in many instances in the struggle that I mentioned to make mechanical conditions in the chest favorable to the circulation. The more respiration races the more muscular labor it costs, and the less it accomplishes with a given amount of labor.[1]

The experiments I have described appear to me to make reasonably clear a much discussed question which has been rather obscure and which has a good deal of significance clinically not only because of its individual importance, but because of its bearing on a large subject, that is, the manner in which morphine accomplishes its effects in many cases of respiratory distress,

[1] Kraus' studies of the effects of work upon the respiration of persons with incompetent hearts, and others, have been interpreted as showing that in cardiac cases the amplitude of respiration increases under moderate strain as much as, or more than, the rate, just as it does in normal persons. In the cases that he studied, which were relatively mild cases of cardiac weakness, the amplitude did at times increase proportionately during work; but this was not always true, and these cases are, at any rate, not comparable with those I refer to in which there is severe incompetency even when there is no unusual strain, and in these amplitude often suffers. Furthermore, in most of Kraus' cardiac cases the amplitude of respiration was abnormally low even when there was no physical strain, and although in some it did increase with work, the result accomplished in such cases with a given increase of amplitude is, because of the greater effect of the dead space in superficial breathing, not as marked as a proportionate increase of amplitude in individuals who start with a normal or even greater degree of amplitude.

and especially in cases in which this distress is due to badly failing heart. It has been very hard to understand why a drug which is not a circulatory stimulant should cause such an evident and often such a rapid improvement in the circulation as it sometimes does. A simple general sedative action and the consequent rest afforded does not seem a sufficient explanation of the striking and rapid change in the circulatory picture often seen, nor are the other explanations that have been offered very satisfactory, and it is most of all difficult to understand why an apparently hopelessly failing respiration should be so greatly relieved by a powerful respiratory depressant. If, however, the centre is in these cases really overexcited and is dulled in sensibility by the administration of morphine, and thus respiration changes its pace to slower, this, as has been generally recognized, would of course greatly reduce muscular labor, but it would do this far more than has been appreciated, and if it would, at the same time, tend to result in respiration actually accomplishing a great deal better its own function and thus help to relieve the respiratory centre itself of strain, and likewise rapidly eliminate an excess of CO_2 (and perhaps other excitants), from the blood, as well as get in more oxygen, the matter would seem to be fairly plain. But if the explanation of the hurried breathing that I have outlined above is correct; if that, is, it is due only partly to a struggle to increase the ventilation in the lungs, partly also to a struggle to make the mechanical conditions easier for the heart, it is apparent that, as is practically a fact, respiratory depressants, such as morphine, must be used in such conditions with great care and judgment. Although both the factors mentioned had been overdoing the matter, a very pronounced slowing of the breathing might readily throw unfavorable strain upon a very incompetent heart by producing too great respiratory changes in blood pressure, even though the contrary source of strain (undue labor from excessive rate) were overcome, and although the ventilation also improved.

Consideration of the points that I have just discussed convinces me that we certainly need to determine as far as we can, in any pathologic disturbance of respiration, when the disturbance is associated with exhaustion of the respiratory centre, and when it

is, on the contrary, due to overstimulation of the centre. The treatment would, in the two cases, be the opposite. I think we may reasonably suspect that we have in many instances been making an error entirely similar to that which we made for years in treating the circulatory failure in acute infectious diseases with the mistaken idea that it was primarily due to excess of blood pressure, whereas it is usually due chiefly to quite the contrary condition. We may, that is, in respiratory distress, equally well have been dealing at times with a condition directly the contrary of what we thought we were treating, and may, especially, very often have been treating an overexcited respiratory centre by still further exciting it. Likewise it appears to me that the effects of the respiratory stimulants need, in purely experimental studies, as well as clinically, to be investigated to determine much more accurately than has been done, their effect on amplitude of respiration as compared with rate, and to determine their actual influence not merely upon tidal ventilation, but, much more important, upon the amount of air that passes in and out of the alveoli. In most of the work that has been done upon them I think their influence upon the actual respiratory function may perhaps have been judged quite as inaccurately as I believe we often judge clinically of the effects of different forms of respiration. Even tracings of the respiration, unless made quantitatively, can give a reliable idea of the effect of a drug upon ventilation only when the effect is so very decided that there is no question of mistake. It is quite possible that we may find that some drugs that are called respiratory stimulants actually lower the efficiency of the function of respiration in some circumstances of disease and even in normal conditions, and the contrary may be true of some so-called respiratory depressants.

Whatever the fate of these suggestions that I have made, I think there can be no doubt that valuable information will be furnished by the coincident study of a large group of variable factors, in further investigations of respiration, clinically as well as in the laboratory. With Benedict's apparatus there is in researches of this kind the great advantage that we can, by relatively simple means, make coincident observations of the CO_2 excretion, the oxygen intake, the tidal and alveolar ventilation, and the efficiency

of each individual respiration. Yandell Henderson also has devised recently a very ingenious and inexpensive instrument that will apparently determine quantitatively the value of individual respiration and give the tidal and alveolar ventilation. One can, of course, add to these studies observations of changes in the circulation and various other factors. From such studies I think we may reasonably hope that in diagnosis and also in treatment we may gain some ground in the attempt to comprehend and benefit symptoms that are frequently even more trying than pain, and much less subject to relief, and that have been vastly less studied than pain.

DISCUSSION

Dr. E. P. Joslin: All those who are interested in experiments with gaseous metabolism will feel deeply grateful to Dr. Edsall for these experiments. The multiplicity for opportunities of error in all experiments on metabolism is so great, and often seems to one not actively engaged in the active part of the experiment so insuperable, any work which renders help in obtaining reliability of results in any series of experiments is of great help. No matter what the character of the respiration was the total amount of oxygen and carbon dioxide absorbed and expired was essentially the same.

Dr. C. F. Hoover: I should like to ask Dr. Edsall whether these experiments are supposed to illustrate the measure of amplitude of ventilation or tidal air?

Dr. D. L. Edsall: I used a bell spirometer. One can measure the exact value in air of each millimeter of the rise and fall of this bell and the needle rises and falls precisely the same amount. I have corroborated this by measuring the movements of the needle and coincidently calibrating by admitting air from calibrated measuring bulbs. It is absolutely quantitative and one can measure each respiration accurately.

Dr. L. F. Barker: I should like to ask Dr. Edsall if he has made any observations indicating any differences in value between breathing which is primarily abdominal and secondarily thoracic and that which is secondarily abdominal and primarily thoracic. One could breathe deeply, or superficially, either way. Teachers of physical culture and of singing lay great

stress upon the importance of abdominal breathing. The importance of this may not be referable to changes in the air; it might be due to the movements in the abdomen. I should be glad to know whether Dr. Edsall's studies throw light upon that point.

Dr. Edsall: In regard to Dr. Barker's question I would say that I have not made observations on that point, but granting that you have the same amount of air going in and out of the chest with either form of breathing the result on the gas exchange would be the same. The two forms of breathing need a good deal of study. I want to point out the fact that other work that I have recently done upon pumping out carbon dioxide by excessive breathing does not, as some persons have thought, reflect upon the accuracy of Benedict and Joslin's work in diabetes. That is another matter. In that work they used as a control Chambers' calorimeter studies. The results of these put their work out of the jurisdiction of criticisms made on the basis of possible differences in breathing. My observations upon the influence of altered breathing on the carbon dioxide output do emphasize very strongly, however, the extreme importance of knowing the ventilation and of using a respiration apparatus that measures the ventilation, as Benedict's present apparatus does.

THE ALVEOLAR AIR AND MINUTE VOLUME OF AIR IN PULMONARY EMPHYSEMA

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This paper will deal with two phases of pulmonary emphysema which have to do with the lung as a respiratory organ apart from the respiratory threshold; minute volume of blood passing through the pulmonary circulation, and influences from the peripheral nerve supply of the respiratory organs.

Patients who apparently have the same degree of emphysema behave in different ways One of my patients had pronounced cyanosis, a respiratory rate 16 to 18 per minute, a minute volume of respired air of 8 liters. The CO_2 content of his alveolar air was 8.55 per cent. This patient did not suffer from air hunger and never had an asthmatic attack.

The second patient presented two phases. On admission to the hospital he was cyanotic. The respiratory rate was 14 per minute. The minute volume of respired air was from 8 to 10 liters. The alveolar air contained 7.2 per cent. of CO_2, and air hunger was pronounced. A few days later conditions improved. He no longer suffered from air hunger, but the respiratory rate was 15 per minute and the minute volume of respired air was 6.38 liters. His alveolar air contained 5.3 per cent. of CO_2 and cyanosis had disappeared. At first glance one would say the lung ventilation was much better during the first period, and, therefore, the real difficulty consisted in an impairment of the lung as the organ of external respiration, *i. e.*, the lung did not afford a good medium for the interchange of carbon dioxide and oxygen between the blood and alveolar air. But we will see later in the discussion the real

difficulty did not consist in an impairment of the respiratory function, but in the ventilatory function. Thus far my observations have been made in cases of marked emphysema which differed much in the clinical symptoms of cyanosis, air hunger, and minute volume of respired air. But when this external respiration was investigated it was found they all suffered from impaired ventilation, but reacted differently. A significant clinical test carried out on the patients substantiate this explanation. None of these patients showed the slightest modification of their symptoms when they breathed an atmosphere of pure oxygen. In other words, they were not suffering from a low oxygen content but from a high carbon dioxide content of their alveolar air, and this can be ascribed only to impaired ventilation.

Patients who suffer from an impairment of the external respiratory function must of necessity get relief from the inhalation of oxygen. This is clearly demonstrated in pulmonary edema and bronchopneumonia of children, whose cyanosis is instantly relieved by the inhalation of oxygen when the real difficulty is impaired ventilation throughout the entire lung. In my personal experience I have known only one emphysematous patient who got relief from the inhalation of oxygen, and I did not have the opportunity of confirming that. I have only the patient's personal testimony, and that must be received with caution from emphysematous and asthmatic persons.

The significance of pathological changes in the infundibular walls of atrophic emphysematous lungs seems doubtful in all of the cases I have studied. Inhalation of oxygen is a good clinical method of differentiating between these two functions, viz., external respiration and lung ventilation.

The early observations on the first patient were made with the aid and direction of Dr. J. J. R. MacLeod, in the physiological laboratory. I wish here to express my thanks and acknowledge the debt of gratitude I owe him for his active aid and instruction in the use of the physiologist's methods of studying respiration.

The method used in studying alveolar air is that described by

Haldane and Priestley.[1] Specimens of the tidal air were procured by Zuntz's method and the analyses of the respired air were made with Haldane's modification of Petterson's[2] apparatus.

The first patient was a man, aged forty-six years, 5 feet 6 inches tall, and weighed 140 pounds when these observations were begun in December, 1910.

The patient had pronounced cyanosis of the lips, nose, ears, tongue, and fingers. Drumstick finger tips were marked. The patient denied ever having had any attack of asthma or experiencing the sense of air hunger. His persistent complaint was a sense of fulness and slight pain over the frontal region and a sense of fulness and pressure in the epigastrium. There was moderate cough and little expectoration. At this time in 1910, the patient worked as presser in a garment factory, and suffered no inconvenience at his work on account of the emphysema.

The heart's apex was in the sixth interspace, and the left border of the heart extended to 14 cm. to the left of the median line in the sixth interspace. The right cardiac border extended 6 cm. to the right of the median line in the fourth interspace. There were no murmurs or accentuation or palpable thrills or palpable closures from any of the heart's valves. The veins of the neck and upper extremities were rather large but no abnormal venous pulsations were visible. There were no signs of any impairment of the mass movement of blood, and Dr. G. N. Stewart[3] estimated the mass movement through the hands, and found it quite normal according to his method.

The lungs were emphysematous. The lower borders were at the ninth rib in the axillary line on both sides and filled the pleural sinus posteriorly.

The costal angle was not enlarged during inspiration, and the anterolateral portion of the thoracic wall from the sixth to the ninth ribs inclusive were drawn toward the median line during inspiration. The epigastrium was protruded, but the lower end of the sternum was drawn toward the vertebra. From a posterior

[1] Jour. Phys., xxxii, 227.
[2] Zeitsch. f. Analyt. Chem., xxv, 467.
[3] Proc. Amer. Phys. Soc., 1911, vol. xxvii, p. 20.

view one sees, however, a distinct increase in the transverse diameter of the base of the thorax in the plane of the posterior axillary line. When the diaphragm occupies a low position the following phenomena are observed during respiration: retraction of the lower end of the sternum, a narrowing or a want of enlargement of the costal angle, and approximation of the hypochondria and protrusion of the epigastrium. These signs were always pronounced in this patient for the two years he was under observation. Auscultation revealed the characteristic prolonged expiratory murmur, and an abundance of coarse and medium dry and an occasional moist rale during inspiration and expiration.

The patient had a moderate cardiac enlargement without any signs of disease of either the pulmonary or aortic arterial systems. No signs of mediastinal disease or disease of the pericardium. The mass movement of blood was normal.

The striking feature about this patient was the cyanosis without dyspnea and without any indication of cardiovascular disease.

The alveolar air was estimated many times over a period of sixteen months, and the CO_2 content was never lower than 7.5 per cent., and was most of the time between 8.1 per cent. and 8.5 per cent.

October 14, 1911, the following four analyses were made of the alveolar air:

1. CO_2 = 8.35 per cent.	3. CO_2 = 8.20 per cent.
O = 11.70 per cent.	O = 12.41 per cent.
2. CO_2 = 8.99 per cent.	4. CO_2 = 8.55 per cent.
O = 12.70 per cent.	O = 11.04 per cent.

The cyanosis and partial pressure of CO_2 in the alveolar air sustained a constant relation to each other.

January 20, 1911, when he was able to be at work and had pronounced cyanosis the alveolar air contained in two analyses 7.3 per cent. and 7.5 per cent. of CO_2.

December 11, 1911, when he was admitted to the hospital complaining of headache and a sense of pressure in the epigastrium, and had a marked increase of the bronchial symptoms and intense

cyanosis the alveolar air contained 9.7 per cent of CO_2 and 10.73 per cent. of oxygen.

On the former occasion when the CO_2 content of the alveolar air was 7.5 per cent. the respiratory rate was 18 per minute and the minute volume was 8.53 liters.

On the latter occasion, when cyanosis was much more intense, the respiratory rate was 19 per minute, the CO_2 content of the alveolar air was 9.7 per cent., and the minute volume was 8.53 liters. He not only tolerated a high CO_2 content of the alveolar air at all times, but tolerated an increase from 7.5 per cent. to 9.7 per cent. without air hunger or any change in the rate or minute volume of respiration. This is a striking result when compared with the intolerance of CO_2 in normal persons, and also when compared with the tolerance of an increase in the CO_2 of the patient's alveolar air after forced breathing and attempts at holding the breath to the breaking point.

March 17, 1911, the following experiments were made:

The alveolar air of Drs. Macleod, Wycoff, and myself contained the following:

J. J. R. M. = 5.67 per cent. CO_2
C. W. = 5.80 per cent. CO_2
C. F. H. = 5.10 per cent. CO_2
Patient—Sam B. = 8.10 per cent. CO_2

We then took the alveolar air of each at the breaking point after holding the breath as long as possible, with the following results:

J. J. R. M. = 6.71 per cent. CO_2
C. W. = 7.27 per cent. CO_2
C. F. H. = 6.71 per cent. CO_2
Patient—Sam B. = 9.00 per cent. and 9.7 per cent. CO_2

Sam B. then breathed as deeply and as rapidly as possible twenty times in thirty seconds. A period of apnea for eighteen seconds followed. Then with the resumption of automatic respiration the alveolar air contained 9.4 per cent. of CO_2. At another time Sam B. breathed twenty-five times in thirty seconds. Apnea for eighteen seconds followed, and with the resumption of automatic respiration the alveolar air contained 10.28 per cent. of CO_2. Nine months later, when his cyanosis was intense, he did

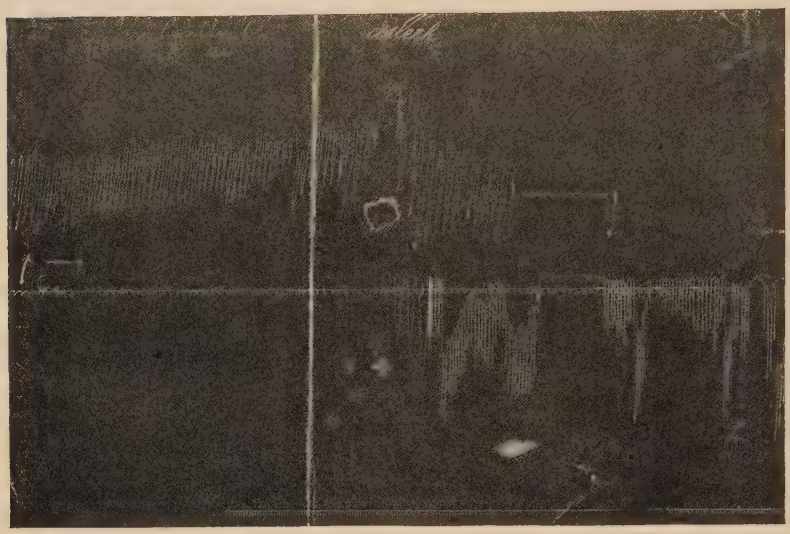
not suffer from air hunger (19 respirations per minute), and the percentage of CO_2 in the alveolar air had attained a percentage which equalled his maximum endurance on former occasions when the CO_2 in his alveolar air was 8.1 per cent. during tranquil breathing.

There was another point of interest in Sam B. relative to his high respiratory threshold: he never had apnea when awake, but when the inhibition of sleep was added to his ordinarily high respiratory threshold, apnea ensued. In this instance, as in instances of slumber apnea associated with sclerosis of the cerebral arteries, the apnea occurred in light sleep.

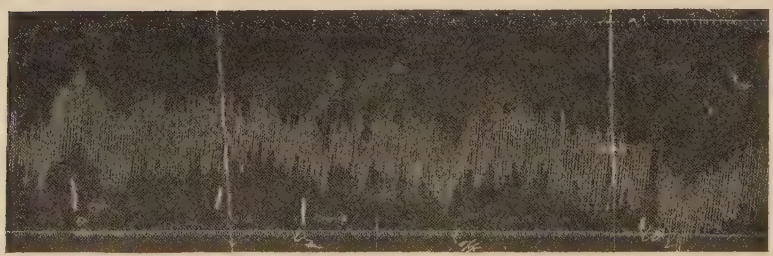
January 27, 1911, Dr. Macleod took a tracing of Sam B.'s respiration in the pneumograph constructed after Haldane's design. The accompanying tracing shows periods of apnea. In the tracing the upward stroke marks the expiratory excursion. In watching the tracing we were at first much concerned to see the cessation of respiration, but as apnea recurred it was observed that respiration ceased as the patient's eyelids closed in sleep. We had repeated opportunities to observe this fact. It was interesting to see the upstroke of the lever to the abscissa mark, the expiratory phase of the thorax as the eyelids fell in sleep. Unlike the slumber apnea of arterial disease the apnea was not followed by hyperpnea and air hunger. As the apnea ceased and the patient simultaneously wakened and resumed automatic respiration the rate and rhythm and depth of the respiratory excursions were resumed as they were up to the moment of apnea.

On the day the tracing in the pneumograph was taken Sam B.'s alveolar air contained 7.5 per cent., 7.9 per cent., and 8 per cent. of CO_2 in three analyses. His minute volume of respired air was 7.9 liters.

December 15, 1911, Sam B.'s alveolar air contained 9.59 per cent. CO_2 and 10.09 per cent. of oxygen. Cyanosis was much more pronounced than on the day the pneumograph tracing was made. When his cyanosis was so pronounced and his alveolar air contained 9.59 per cent. CO_2 he would lie in bed and go to sleep for short intervals of five or ten minutes. It was common for him to go to sleep five or six times in an hour, but when he



Read from left to right. The upstroke marks the expiratory excursion. The arrests of respiration in the expiratory phase mark the points at which the patient went to sleep.



Read from left to right. The upstroke marks the expiratory excursion. Note that oxygen inhalation did not modify the respiration, whereas the excursions increased the instant some carbon dioxide was introduced into the respired air.

went to sleep he did not cease breathing. It seems the partial pressure of CO_2 was so high that apnea was never allowed in his moments of slumber. During this period his respiratory rate was 27 per minute, but the minute volume was only 6.566 liters. When asked if he suffered from a sense of air hunger he always protested that he had no difficulty in breathing, and said his only trouble was headache and a sense of pressure in the epigastrium. The man was really suffering from carbon-dioxide poisoning. During the winter and spring we repeatedly gave him large amounts of oxygen to breathe, and although the partial pressure of oxygen in the air he breathed was as high as 50 per cent., it never modified the respiration in any way. We have in this patient a heightened respiratory threshold with an alveolar air rich in CO_2 and poor in oxygen, without hyperpnea and with a normal minute volume of respired air. The lung ventilation is therefore apparent, but not real.

The tidal air was then estimated according to Zuntz's method, and the alveolar air was analyzed at the same time. It is clear that the CO_2 given off must come from the alveolar air, and as Haldane suggests, if we know the minute volume of respired air and its content of CO_2, and also the content of CO_2 in the alveolar air, then we have a formula for estimating the proportion of alveolar to tidal air. I have a minute volume of 8.16 liters. This minute volume of air contains 3.28 per cent. of CO_2 and my alveolar air contains 5.05 per cent. of CO_2. We have the formula:

$$3.28 \times 8.16 \text{ liters} = 5.05 \times x$$

$$\text{Therefore } \frac{3.28 \times 8.16}{5.05} = \text{alveolar air}$$

December 8, 1911, the Zuntz apparatus was used for collecting a sample of air from Sam B.:

Time of collection	= 10.25 minutes	
Rate of respiration	= 12 per minute	
Minute volume	= 9.16 liters	
Zuntz specimen	CO_2 = 4.23 per cent.	or 0.387 liter per minute
	O = 17.45 per cent.	
Alveolar air	CO_2 = 8.30 per cent.	
	O = 10.90 per cent.	

The alveolar air equals 4.66 liters, which is 50.9 per cent. of the minute volume. The respiratory quotient equals 1.2.

December 11, 1911, Sam B. was more cyanotic than at the time the previous specimen was taken. His diet also was more liberal.

Time of collection	= 11	minutes
Rate of respiration	= 19.10	per minute
Minute volume	= 8.53	liters
Zuntz specimen CO_2	= 3.84	per cent. or 0.327 liter per minute
Zuntz specimen O	= 15.94	per cent.
Alveolar air CO_2	= 9.77	per cent.
Alveolar air O	= 10.73	per cent.
Alveolar air	= 3.35	liters or 39.2 per cent. of the minute volume
Respiratory quotient	= 0.70	

Another Zuntz specimen taken the same day:

Time of collection	= 10	minutes
Average rate of respiration	= 27	per minute
Minute volume	= 8.73	liters
CO_2	= 3.94	per cent. or 0.343 liter per minute
O	= 16.90	per cent. or 0.375 liter absorbed per minute
Alveolar air	= 3.52	liters or 40.3 per cent. of minute volume
Respiratory quotient	= 0.90	

December 15, 1911. Cyanosis pronounced.

Time of collection	= 12	minutes	
Minute volume	= 6.566	liters	
Rate of respiration	= 27	per minute	
Zuntz specimen CO_2	= 5.210	per cent. per minute	= 0.342 liter
Zuntz specimen O	= 13.495	per cent. absorbed per minute	= 0.541 liter
Alveolar air CO_2	= 9.590	per cent.	
Alveolar air O	= 10.090	per cent.	
The alveolar air	= 3.567	liters or 54 per cent. of minute volume	
Respiratory quotient	= 0.640		

Compare the results with the same apparatus in my own respiration and we find that my alveolar air varied from 64 to 82 per cent. of the minute volume. When my respiratory rate was 10 per minute the alveolar air constituted from 64 to 77 per cent. of the tidal air. Whereas Sam B.'s alveolar air constituted only 50.9 per cent. of the tidal air when he was breathing twelve times per minute and had a minute volume of 9.16 liters.

It is obvious that if the minute volume remains the same a slower rate of respiration will give a larger percentage of alveolar

air in the minute volume than when the rate of respiration is increased.

December 15, 1911, a Zuntz specimen was taken from me with the following results:

Time of collection = 12 minutes
Respiratory rate = 10 per minute
Minute volume = 8.16 liters

This specimen contained:

CO_2 = 3.28 per cent.
O = 17.27 per cent.

The alveolar air taken at the same time contained:

CO_2 = 5.05 per cent.
O = 14.90 per cent.
Respiratory quotient = 0.87

The alveolar air, therefore, equalled 64.8 per cent. of the tidal air.

From C. F. H.—another specimen on December 19, 1911.

Time of collection = 11 minutes
Respiratory rate = 10 per minute
Minute volume = 8.081 liters

This specimen contained:

CO_2 = 3.780 per minute
O = 16.225

The alveolar air contained:

CO_2 = 4.86 per cent.
O = 15.24 per cent.
Respiratory quotient = 0.75

The alveolar air constituted 77.7 per cent. of the minute volume.

At a later date the experiment was tried of breathing as nearly fifteen times per minute as I could. The alveolar air at this time in July, 1912, a warm day, contained 4.5 per cent. CO_2.

The following are the results from three Zuntz specimens from C. F. H.:

No. 1.

Time of collection	=	12 minutes
Minute volume	=	8.13 liters
Respiratory rate	=	15.10 per minute
CO_2	=	2.70 per cent.
Alveolar air	=	60.00 per cent.
CO_2 per minute	=	222.00 c.c.

No. 2.

Time of collection	=	8 minutes
Minute volume	=	9.14 liters
Respiratory rate	=	16.00 per minute
CO_2	=	2.70 per cent.
Alveolar air	=	59.90 per cent.
CO_2 per minute	=	246.00 c.c.

No. 3.

Time of collection	=	7 minutes
Minute volume	=	9.76 liters
Respiratory rate	=	16.30 per minute
CO_2	=	2.40 per cent.
Alveolar air	=	53.30 per cent.
CO_2 per minute	=	234.00 c.c.

From these results it seems quite clear that the dead space in emphysema must be increased. There must be considerable expansion of the lung between the bronchioles and the large bronchi, otherwise I can see no explanation for the fact that in emphysema the alveolar air (which in this patient was so rich in CO_2) should constitute such a small percentage of the tidal air when the rate of respiration and the minute volume are normal or what conform to comfortable respiration and ventilation in a normal person.

In the case of Sam B. the alveolar air was rich in CO_2 and poor in oxygen. So the question naturally arose as to whether the cyanosis was due to an excess of CO_2 or diminution in oxygen.

It was formerly shown that a great increase in the partial pressure of oxygen did not modify the cyanosis nor the rate or apparent minute volume. An oxygen tank was connected with a rubber bag which communicated with the Zuntz apparatus. In this manner the patient was enabled to breathe an atmosphere of pure oxygen. A sample was taken from the tank which yielded 93 per cent. of oxygen on analysis.

Sam B. had a respiratory rate of 22 per minute on this day (April 19, 1911), and maintained the same rate during the time the Zuntz specimen was collected. The time of collection was eight minutes. The minute volume was 8.431 liters. The sample contained 2.5 per cent. of CO_2.

Another specimen was collected during ten minutes and forty seconds. The minute volume was 9.510 liters. The respiratory rate varied between 20 and 25 per minute.

The sample contained:

CO_2 = 2.9 per cent.
O = 91.2 per cent.

In spite of the fact that his alveolæ were constantly filled with oxygen the cyanosis remained the same. We then took a Zuntz specimen from Sam B. when he was breathing atmospheric air, with the following results:

Time of collection	= 8	minutes	
Minute volume	= 7.895	liters	
Respiratory rate	= 22	per minute	
Zuntz specimen	CO_2 = 2.21	per cent.	
	O = 19.50	per cent.	
Alveolar air	CO_2 = 8.05	per cent.	
	O = 12.30	per cent.	

Sam B. was then instructed to breathe twelve times as deeply and rapidly as he could. At the end of this forced breathing the alveolar air contained:

CO_2 = 6.79 per cent.
O = 15.71 per cent.

During March, 1912, the opportunity was given to prove the interpretation given Sam B.'s cyanosis and emphysema in a patient who entered the hospital with pronounced pulmonary emphysema, air hunger, and cyanosis. The cyanosis was not nearly so intense as in the case of Sam B., but the lungs extended downward to the seventh, ninth, and eleventh ribs respectively in the nipple, axillary, and scapular lines. Furthermore, the central tendon of the diaphragm occupied a low position, as evidenced by the downward displacement of the liver and the strong approximation of the

hypochondria toward the median line during inspiration. Although the patient breathed laboriously, the respiratory rate was 15 per minute, and the same rate was maintained while breathing through the Zuntz valves. With the first trial breathing was more laborious than when the apparatus was not used, consequently the minute volume was large and a large amount of CO_2 was given off.

First experiment on A. S., March 29, 1912.

Time of collection		= 15	minutes
Respiratory rate		= 14	per minute
Minute volume		= 10.15	liters
Zuntz specimen	CO_2	= 2.37	per cent.
	O	= 18.10	per cent.
Alveolar air	CO_2	= 7.20	per cent.
	O	= 14.30	per cent.
Respiratory quotient		= 0.79	
CO_2 per minute		= 0.241	liters
Alveolar air		= 3.341	liters or 31.8 per cent. of the minute volume

After further trials, A. S. learned to breathe through the apparatus with less effort. The following test is a specimen taken when the minute volume was less, but the respiratory rate was the same, viz., 14 per minute:

Time of collection		= 11	minutes
Respiratory rate		= 14	per minute
Minute volume		= 8.059	liters
Zuntz specimen	CO_2	= 2.160	per cent.
	O	= 18.700	per cent.
Alveolar air	CO_2	= 7.440	per cent.
	O	= 12.440	per cent.
Total CO_2 per minute		= 0.174	liters
Respiratory quotient		= 0.960	
Alveolar air		= 2.339	liters or 29.7 per cent. of the minute volume

A few days later A. S. was much more comfortable. There was no cyanosis, but the respiratory rate remained the same as when the patient was cyanotic. The lower borders of the lungs were still at the seventh, ninth, and eleventh ribs, but the central tendon of the diaphragm was evidently not so low. Although the costal angle did not widen during inspiration there was not the strong approximation of the hypochondria as formerly when cyanosis was present and the bronchial wheezing was more pronounced.

Third specimen from A. S., April 1, 1912.

While the Zuntz specimen was collected the patient breathed easily at the rate of 15 per minute.

Time of collection		= 13	minutes
Respiratory rate		= 15	per minute
Minute volume		= 6.380	liters
Zuntz specimen	CO_2	= 2.700	per cent.
	O	= 18.400	per cent.
Alveolar air	CO_2	= 5.300	per cent.
	O	= 15.500	per cent.
Respiratory quotient		= 1.000	
CO_2 in minute volume		= 0.172	liters
Alveolar air		= 3.250	liters or 50.9 per cent. of the minute volume

When the third specimen was taken it must be observed that the respiratory rate was 15 as compared with 14 in the second specimen, and although the minute volume in the third specimen was 6.38 liters as compared with 8.059 liters in the second specimen, the lung ventilation was much better, for the alveolar air constituted 50.9 per cent. of the minute volume in the third specimen and only 29.7 per cent. in the second specimen. Moreover, at the time the third specimen was taken the patient had no cyanosis and the alveolar air contained 5.3 per cent. of CO_2. When the second specimen was taken cyanosis was pronounced and the alveolar air contained 7.44 per cent. CO_2. With a lesser minute volume and the same respiratory rate there was much better lung ventilation.

The corollary from the experiment is that the respiratory rate and minute volume (when studied apart from the CO_2 content of the tidal and alveolar air) are no guides for estimating the real ventilation of the lung when bronchiolar volume is a factor under consideration.

Another mode of reaction is exemplified in the following case: Mrs. L. entered Lakeside Hospital in June, 1912. This patient was a small thin woman who weighed 110 pounds. For two years she has had dyspnea, and could do very little work on account of her respiratory limitations. The heart was not enlarged, there were no signs of any cardiovascular disease, *i. e.*, disease of the heart or aortic or pulmonary circulation. There were no evidences of any mediastinal disease. The lungs were emphysematous, and were situated at the seventh, tenth, and eleventh ribs respectively

in the nipple, axillary, and scapular lines. During inspiration the lower end of the sternum was retracted and the epigastrium protruded. The costal angle was not enlarged during inspiration. The costal borders to the eighth ribs did not diverge during inspiration, but below the eighth ribs there was marked respiratory divergence of the costal borders, so the base of the thoracic cage had a marked increase in the transverse diameter during inspiration. Mrs. L. was not cyanotic, but she complained of air hunger and had a respiratory rate of 26 during her stay of three weeks in the hospital. There was no pronounced cyanosis, but at times there was a suggestion of cyanosis in the cheeks; but the fingers, ears, or tongue never revealed any pronounced cyanosis. This patient evidently retained her normal respiratory threshold, and therefore breathed rapidly to compensate for poor alveolar ventilation. Consequently in this patient there were two factors which contributed to lowering the percentage of alveolar air in the minute volume of respired air, viz., emphysema and a rapid respiratory rate.

Zuntz specimens taken from Mrs. L. gave the following results:

Time of collection		=	9 minutes
Respiratory rate		=	25.11 per minute
Minute volume		=	7.80 liters
Zuntz specimen	CO_2	=	1.48 per cent.
	O	=	19.30 per cent.
Alveolar air	CO_2	=	5.55 per cent.
	O	=	13.44 per cent.
Respiratory quotient		=	0.80
Alveolar air		=	26.60 per cent. of minute volume
CO_2 per minute		=	115.00 c.c.

Another specimen showed the alveolar air to equal 29.4 per cent. of the minute volume.

These three patients all present some signs which they have in common, and in other respects they greatly differ. All had increased pulmonary volume, and indeed so far as objective signs of pulmonary volume are concerned they all had their lungs in the maximum inspiratory volume. All had the characteristic skodaic resonance and all had the prolonged expiratory phase.

Sam B. had much more evidence of bronchitis than A. S. or Mrs. L. Sam B. was always cyanotic. A. S. had cyanosis only

during his first week in the hospital. Mrs. L. never had cyanosis. Sam B. never suffered air hunger. A. S. had air hunger only during the period of cyanosis. Mrs. L. was never free from air hunger.

If we compare the results in Mrs. L. with the results in A. S. there is at first glance apparently a marked inconsistency in the results obtained in the two patients.

The second specimen from A. S. gave a minute volume of 8.059 liters. His alveolar air contained 7.44 per cent. of CO_2.

Mrs. L. showed in repeated tests a minute volume a little less than 8 liters. Her alveolar air always contained between 5.5 per cent. and 6 per cent. of CO_2. Her alveolar air ranged between 26 per cent. and 30 per cent. of the minute volume. But A. S. was cyanotic at the test referred to, and Mrs. L. was never cyanotic. There was this difference, however: A. S. had a respiratory rate of only 15 per minute, whereas Mrs. L. had a respiratory rate which was constantly from 23 to 26 per minute. That the lung ventilation was better in Mrs. L. must be granted, because she was not cyanotic and her alveolar air had a CO_2 content of from 5.5 per cent. to 6 per cent. The fact that her alveolar air constantly composed only 26 per cent. to 30 per cent. the minute volume (as in A. S.) must then be due to the increased respiratory rate.

I have compared my own lung ventilation with the ventilation of emphysematous lungs when I employed the same respiratory rate and minute volume which the emphysematous patients had, and found my alveolar air under these conditions represented 60 per cent. of the alveolar air as against 30 per cent. in the emphysematous patients. But this comparative test of respiratory rate and minute volume and alveolar air was a comparison between a healthy lung and emphysematous patients who were cyanotic. I therefore wished to compare my lung ventilation with that of an emphysematous patient who was not cyanotic.

I then took a Zuntz specimen from myself when I breathed twenty-five times per minute, and endeavored to breathe so that the minute volume would be the same as in Mrs. L. This was accomplished by setting up a mirror before the dial of the spirometer, so that the excursion of the indicator could be seen, and thus at will the amount of each respiratory excursion could be

made to conform to the desired minute volume. An assistant beat time, so the number of respirations could be timed for exactly 25 respirations per minute. Thus the minute volume respiration of Mrs. L. was accurately imitated in my own breathing. While this artificial respiratory rate and minute volume were maintained, it was desirable also to know what the CO_2 content of the alveolar air might be. For this purpose the mouth-piece of the Zuntz apparatus was fitted with a lateral opening through which a sample of alveolar air could be procured at the end of the experiment. It was necessary to know the oxygen and carbonic acid content not only for estimating the proportion of alveolar air to the minute volume of air, but also, to see if the percentage of carbonic acid in the alveolar air conformed to the sense of air hunger which prevailed during the time the Zuntz specimen was being taken. The alveolar air was taken on the end of the last expiration of the seven minutes during which the Zuntz specimen was taken.

Time of collection	= 7	minutes
Respiratory rate	= 25	per minute
Minute volume	= 7.40	liters
Respiratory quotient	= 0.60	
Alveolar air of the minute volume	= 39.70	per cent.
Zuntz specimen CO_2	= 2.60	per cent.
Zuntz specimen O	= 17.30	per cent.
Alveolar air CO_2	= 6.70	per cent.
Alveolar air O	= 13.12	per cent.

Another trial was made during which the sense of air hunger was not so severe as during the above test, but the sense of air hunger was pronounced.

Time of collection	= 8	minutes
Respiratory rate	= 25	per minute
Minute volume	= 7.57	liters
Respiratory quotient	= 0.65	
Alveolar air of the minute volume	= 44.90	per cent.
Zuntz specimen CO_2	= 2.08	per cent.
Zuntz specimen O	= 17.00	per cent.
Alveolar air CO_2	= 6.27	per cent.
Alveolar air O	= 13.73	per cent.

When the results are compared with those of Mrs. L. it will be noted that the alveolar air represented a larger portion of the

minute volume than in the case of Mrs. L., and although my sense of air hunger was pronounced, as was also quite evident in Mrs. L., my alveolar air at the end of the experiment contained 6.7 per cent. and 6.2 per cent. of CO_2. Whereas Mrs. L.'s alveolar air contained only 5.5 per cent. This seemed too low to be consistent with her sense of air hunger, the degree of emphysema, and also the suggestion of cyanosis in her face, which amounted to a slightly dusky hue, although, as has been stated, there never was pronounced cyanosis of the fingers, ears, or tongue. The estimates of Mrs. L.'s alveolar volume compared with her minute volume of air always proved the lung ventilation to be poor, as has been shown when I employed the same respiratory rate and minute volume as Mrs. L. My alveolar air represented 10 per cent. more of the minute volume than was the case with Mrs. L. In spite of this comparison it never seemed to me that we quite got the alveolar air of Mrs. L. The degree of emphysema and air hunger always seemed inconsistent with such a moderate elevation of partial pressure in the CO_2 of her alveolar air. From our former experiences with emphysema too it seemed reasonable to expect a better tolerance of such an elevation of CO_2 content of the alveolar air in a patient who had emphysema continuously for two years. I mean by this the sense of air hunger was disproportionately great for the CO_2 content of the alveolar air as estimated from a specimen of air procured at the end of a strong, quick, voluntary expiration.

Mrs. L. was a frail woman with a thin thorax, which could be easily compressed, so we thought the real alveolar air may be better procured by compressing the thorax at the same time a voluntary expiratory effort was made.

The following experiments were then made:

A Zuntz specimen was taken for eleven minutes.

Minute volume	=	7.522 liters
Respiratory rate	=	22.500 per minute
Zuntz specimen CO_2	=	1.900 per cent.
Zuntz specimen O	=	19.000 per cent.

The alveolar air was then taken at the end of a voluntary expiration. The first specimen contained 5.7 per cent. of CO_2. The second specimen 6.1 per cent. of CO_2.

The patient breathed through the tube used in procuring alveolar air, and then as she was instructed to blow, her nose was closed by one assistant, another seated behind the patient forcibly compressed the thorax as the forced expiration was made, and immediately the specimen of air was taken. This was all done so quickly that the time factor could not be responsible for a high CO_2 content. The specimen was procured as promptly as at other times, when there was no compression of the thorax employed. The alveolar air procured in this manner had a CO_2 content of 6.7 per cent., which seemed consistent with the whole clinical picture. The patient, A. S., had a CO_2 content of 7.2 per cent. in his alveolar air when he was cyanotic and 5.3 per cent. a few days later when he was not cyanotic.

If the percentage of alveolar air in Mrs. L. is estimated on the basis of 6.7 per cent. CO_2, then the alveolar air will constitute 28.3 per cent. of the minute volume. If the estimate is made on the basis of 6.1 per cent. the alveolar air constitutes 31.1 per cent. of the minute volume.

This method of compressing the thorax was employed in the case of Sam B., whose alveolar air at the time contained 8.3 per cent. of CO_2 and the results obtained were the same as when no compression was employed. His thorax was unyielding and the trunk muscles were powerful.

The same results were obtained in two healthy well-muscled men. It seems probable that in the case of Mrs. L. that 6.7 per cent. more nearly represents the CO_2 content of her alveolar air than 5.3 per cent., or 6.1 per cent., which were the minimum and maximum percentages obtained in a dozen analyses made at different times.

This method of estimating the lung ventilation proved to be of service in studying the case of a man, aged seventy-one years, who gave a history of air hunger which existed two months before entering Lakeside Hospital.

This patient (L. S.) was a powerful man, with a large and resistant thoracic cage. The only complaint the patient had was constant air hunger and frequent attacks of hyperpnea, which wakened him at night. There was no cyanosis or evidences of any

cardiovascular disease. There was marked retraction of the costal borders and narrowing of the costal angle during inspiration. The lungs were voluminous. The finger nails were ridged, and he gave a clear history of gout which had been diagnosticated by several physicians.

At the base of the right thorax in the axillary line there was movable dulness, which was not pronounced, but gave rise to the suspicion of fluid in the right pleural cavity. Although the lungs were voluminous (at the ninth rib in the axillary lines), and the respiratory movements of the hyperchondria betrayed a low position of the central tendon of the diaphragm, yet there were no signs of bronchitis.

The real question in this case was to account for the low position of the central tendon of the diaphragm. The CO_2 of his alveolar air was first determined from specimens procured at the end of a forced expiration and found to be 3.7 per cent., 3.8 per cent., and 3.9 per cent. in three specimens. Compression was then employed at the end of expiration and the CO_2 content was 3.5 per cent., 3.7 per cent., and 4.2 per cent. in three specimens.

A Zuntz specimen was then taken for nine minutes.

Minute volume	=	7.405 liters
Respiratory rate	=	16 per minute
Air sample CO_2	=	1.900 per cent.
Air sample O	=	19.000 per cent.

Alveolar air taken directly after the Zuntz specimen was finished gave a CO_2 content of 3.2 per cent., and 3.3 per cent. in two specimens.

The alveolar air equalled 58 per cent. of the minute volume, therefore the low position of the diaphragm could not be due to emphysema of bronchial origin.

A skiagram of the thorax was then made and a tumor in the mediastinum directly behind the heart was clearly definable, which displaced the central tendon downward. An exploratory needle was then inserted and a thin layer of fluid was located at the base of the right thorax. The fluid was not bloody, but contained a few red cells and many mononuclear cells. The patient left the hospital, but the skiagram justified the diagnosis of a

mediastinal tumor, which simulated bronchial emphysema by its displacement of the central tendon of the diaphragm. Had not the estimates of the minute volume and alveolar air been made we would have overlooked the real disease and regarded the whole difficulty as bronchial emphysema with nocturnal asthma!

In the cases of Sam B. and Mrs. L., atropine and adrenalin were given subcutaneously to see if the percentage of CO_2 in their alveolar air could be modified. One thirty-fifth grain of atropine sulphate and 20 minims of 1 to 1000 adrenalin were given in each case. The CO_2 content of the alveolar air remained the same in both patients before and after the use of both atropine and adrenalin.

The essential result of these observations of pulmonary emphysema is the direct evidence that in emphysema the patient suffers from an impaired alveolar ventilation of the lung and not from an impairment of the lung as the organ of external respiration. Furthermore, the evidence seems very conclusive that the alveolar air constitutes a diminished part of the minute volume of air. So the minute volume in any given case of emphysema is not a measure of alveolar ventilation. This diminution of the proportion of alveolar air must be due to an increase of the dead space. How can we account for an increase of the dead space in pulmonary emphysema? Can the increase of the dead space be explained best by bronchiolar spasm, bronchiolar atony, or swelling of the bronchiolar mucosa? Bronchiolar atony, that is, an elongation and broadening of the bronchioles, seems the most consistent with an increase of the dead space. Bronchiolar spasm, or swelling of the bronchiolar mucosa, could give an increase of the dead space only by an inspiratory enlargement of that portion of the air passage which lies between the infundibula and the larynx.

I hope in the near future to present the evidence from some completed animal experiments which will throw light on this question.

In conclusion, I wish to thank Dr. Chauncy Wyckoff, former resident of Lakeside Hospital, and Dr. L. H. Taylor, resident physician at Lakeside Hospital, for their valuable assistance in this work.

DISCUSSION

Dr. David L. Edsall: With the Benedict apparatus there is a great tendency for the patient to fall asleep. I became so accustomed to pauses occurring at the height of inspiration as the subjects of my experiments were falling asleep that I soon became able to tell when they were about to go asleep and not wanting the subject to go asleep, for fear he would open his mouth and admit outer air, I would shout at him to wake up. They usually went to sleep with full inspiration. In one of the tracings I passed around the man was on 90 per cent. of oxygen and there was a very peculiar phenomenon, without any tendency to sleep. He had periods of apnea, for as much as three-quarters of a minute, but always at full inspiration. Why these things occurred I do not know. I would like to inqure what Dr. Hoover found in regard to the accuracy of records of ventilation with Haldane's body plethysmograph, as compared with direct meter measurements.

Dr. C. F. Hoover: It is extremely accurate. The slightest movement is recorded. The quantitative excursion of your lever records any movement, if the man breathes the least bit.

Dr. D. L. Edsall: Does it correspond quantitatively with direct meter measurements?

Dr. Hoover: I never recorded meter movements on smoked paper.

Dr. Edsall: I did not mean recording meter movements on smoked paper, but whether the two correspond well, the breathing rate and record.

Dr. Hoover: I think it records very accurately for the actual tidal air.

Dr. S. J. Meltzer: Was the cyanosis extensive and visible also on the mucous membrane?

Dr. Hoover: Yes, his tongue was quite blue.

Dr. S. J. Meltzer: From what source did the man get his carbon dioxide in these larger quantities?

Dr. T. C. Janeway: Did you make a spectroscopic study of his blood as to the presence of sulph- or methemoglobin. Also did the man have polycythemia? The occurrence of bronchitis and cyanosis without dyspnea seems to me a bit unusual.

Dr. Hoover: There was a slight polycythemia, not great. In answer to Dr. Meltzer's question, we could show that really in this man the dead air space was very much increased. With the Zuntz apparatus we got the percentage of alveolar air in his tidal air. In his tidal air we used the Zuntz apparatus and we found that the alveolar air represented only about 29 to 30 per cent. of his tidal air, whereas in my case it would vary with the type of breathing from 65 to 80 per cent. The difficulty in my patient was that though his tidal air was normal the percentage of carbon dioxide in his alveolar air was extremely large and in his tidal air was low. We had him breathe an atmosphere of pure oxygen to answer the question of what caused the cyanosis, whether it were due to a diminution in the quantity of oxygen or an excess of carbon dioxide. We connected him with the oxygen and found we could recover 93 per cent. of pure oxygen. He inhaled for fifteen minutes nothing but oxygen and his tidal air by actual analysis contained a little above 92 per cent. His cyanosis was not the least bit modified. It is simply a problem of ventilating the infundibulum. If we estimate the tidal air as ventilation of the infundibulum we make a mistake. The problem is to get the carbon dioxide out of the infundibulum. I remember a patient, an extreme cyanotic, who had a pulmonary emphysema. This man was compelled to travel a great deal, and would never travel without a small tank of oxygen in his berth. If he had to go without the oxygen he was miserable, he could not sleep. If he had the tank of oxygen he could sleep through the night. I think the oxygen did him very little real good. It was not oxygen into his infundibulum he needed, but it was the problem of getting carbon dioxide out. Another patient who had presented cyanosis and a low position of the diaphragm was quite cyanotic. By estimating his alveolar air and the total amount of carbon dioxide eliminated in a given period when suffering from air hunger, the alveolar air represented 29 per cent. only of his tidal air. A few days later when no longer cyanotic, when his lungs had emphysema and had no longer the narrowing of the costal angle and traction of the hypochondria when we measured his alveolar and tidal air, we found that the alveolar air had risen to 52 per cent. of his tidal air. Whereas when cyanotic 29 per cent. was tidal air. We must not always assume that the low position of the central tendineæ is a guide to emphysema. The central tendineæ may be pushed down in a patient with mitral insufficiency who is not cyanotic.

FURTHER REMARKS ON THE TREATMENT OF NEPHRITIS

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I. INTRODUCTION

It is now more than a year since, on the basis of our colloid-chemical views of the nature and the cause of nephritis, the first attempt was made to utilize these views for the relief of clinical cases. A year ago James J. Hogan tried for the first time to relieve an acute nephritis with total suppression of urine by injecting into the patient a hypertonic sodium chloride solution containing sodium carbonate. Since that time the simple principles of treatment that we have proposed have been tried on many private and hospital patients, and so it has been possible to arrive at some conclusions regarding their actual value. We wish to discuss this question in brief in the following pages. At the same time we wish to satisfy the request of a number of medical men to outline in greater detail than we have so far done, the best way to proceed, in our judgment, in the handling of these cases, and cite some case histories to illustrate what we have to say.

For a detailed statement of our colloid-chemical views on the nature and cause of nephritis, we must refer the interested reader to our previous discussions of this subject.[1] Briefly formulated, we may express them as follows: All the signs and symptoms of a nephritis are colloid-chemical in nature, and due (in major part) to a common cause, the abnormal production or accumulation of acid in the kidney. The action of the acid in making the protein colloids of the kidney go into solution in the urine explains the

[1] Edema, 191, New York, 1910; Kolloid Zeitschr., viii, 202 (1911); Kolloidchemische Beihefte, ii, 304 (1911); Ohio State Medical Journal, August, 1911; a monograph dealing specifically with this subject constitutes: Nephritis, New York, 1912.

albuminuria; its action in making the kidney colloids swell causes the increase in the size of the kidney; its action in precipitating a second colloid makes the change of color (graying) in the kidney. Since the (colloidal) cement substance that holds the kidney parenchyma fast to its supporting tissue dissolves more easily than that which binds the cells to each other, the cells slip out of the uriniferous tubules in groups called "casts." The casts may be cellular, granular, or hyaline, depending solely upon the state of the colloids found in them, this being in its turn determined by the amount of acid, salt, etc., present in the blood, the kidney, or the urine. The changes in the output of water are referable to a disturbance in the normal dynamic relationships existing between the concentration of water and acid found in the blood, and the water and acid found in the kidney parenchyma. The changes in the secretion of dissolved substances are, from an absolute standpoint, referable to the absolute decrease in the amount of water secreted by the nephritic kidney; from a relative standpoint, to a change in the adsorption characteristics of the blood and kidney colloids as influenced by such a change in the composition of the kidney as is determined by an abnormal production or accumulation of acid in this organ.

We maintain that all nephritides are parenchymatous nephritides. These parenchymatous nephritides may be general (involve the whole kidney) as is the case in the ordinary acute or chronic intoxications; or local (involve only parts of the kidney) as is the case in the so-called chronic interstitial nephritides associated with cardiovascular changes (primarily contracted kidneys), where, in consequence of changes in the bloodvessels one fragment after another of the kidney is destroyed and replaced by connective tissue. Between these spots of parenchymatous nephritis the kidney substance is largely normal, and so in this type of kidney disease the decrease in urinary output, the albuminuria, the casts, etc., may be largely absent.

We wish to direct attention to two more points in our colloid-chemical conception of nephritis in order to render clearer the purposes of our therapy. The first of these has to do with the edema that is so frequently an accompaniment of nephritis. It is generally

held that a patient has a generalized edema *because* he has nephritis; in other words, the generalized edema is held to be secondary to the kidney disease. We think this conclusion to be, in the main, incorrect. If the edema were secondary to loss of kidney function, then we should be able to produce a generalized edema experimentally most rapidly by complete removal of the kidneys. As a matter of fact, nephrectomized animals either develop no edema at all or only a very slight one, as compared with the edema developed, for instance, after the injection of uranium nitrate. This shows clearly that the edema of the tissues generally and the edema of the kidney (nephritis) arise *simultaneously* and from the same cause.

Another point that we wish to emphasize is that there is no free water in the body—it exists in all the tissues and body fluids only in combination (as hydration water) with the various (hydrophilic) colloids present. When any free water appears in the body, it is quickly removed by one of the secretory organs (such as the kidney). Conversely, it is impossible to get any secretion except as we furnish the secreting organ free water. The kidney can secrete urine only as we give it water from which to make this urine.

What our text-books list as "causes" of nephritis—excessive muscular work, heart disease, lung disease, anemia, carbon monoxide posioning, exposure to cold, interference with the blood supply to all or to a part of the kidney (pressure on the kidney vessels, arteriosclerosis, thrombosis, embolism), intoxication of the kidney parenchyma with a toxin, chloroform, ether, arsenic, uranium, chromium, lead, phosphorus, amyl nitrite, etc., restriction of salt consumption or excessive consumption of water low in salts—all gain their etiological importance in the problem only because they represent methods which, by direct or indirect means make for an abnormal production or accumulation of acid in the kidney.

These remarks will suffice to indicate why we have formulated the general rule for the prophylaxis and treatment of nephritis in these terms. *As far as possible, avoid every condition that favors the abnormal production or accumulation of acid in the kidney.*

The aggressiveness and persistence with which we try to follow this simple rule, and the results that we shall get by doing it, evidently depend upon the condition or combination of pathological conditions that our patient may have developed, and which we hold responsible for the abnormal production or accumulation of acid in his kidneys. Very evidently an anesthesia nephritis with suppression of urine will call for a more aggressive therapy than a nephritis secondary to a slowly progressing arteriosclerosis. On the other hand, if we succeed in getting our first nephritic over his immediate kidney symptoms, we may make a hopeful prognosis, for when he has exhaled his anesthetic he has rid himself of the condition that was responsible for the abnormal acid content in his kidneys. But in our second nephritic so hopeful a prognosis against all time cannot be made, for while we may also benefit him, he continues to carry the original condition that brought him to us—his arteriosclerosis—even after we have treated him.

Our rule for the treatment of the threatened or established case of nephritis may be summarized in these words: *Give alkali, salts, and water.* The reasons for this are, in brief, as follows: The *alkali* is given in order to neutralize the acid present in abnormal amount in the kidney (and in the other edematous organs of the body) and to which we have attributed the changes in the colloids of the kidney which give us our clinical picture of nephritis. The *salts* are indicated (and sodium chloride is no exception) because the various changes induced in such colloids as constitute the kidney by the action of acid upon them, are counteracted by adding to such acid any salt, even a neutral salt.[1] We need to give *water* in order to have this present in the body over and above the amount necessary to saturate all the body colloids; otherwise we shall have no "free water" left over out of which to make urine.

With this let us pass to a consideration of the specific instructions which we think it well to give in the treatment of any clinical case of nephritis.

[1] See Martin H. Fischer and Gertrude Moore, Amer. Jour. Physiol., 1907, xx, 330; Kolloid Zeitschr., 1909, v, 197; Martin H. Fischer, Pflüger's Arch., 1908, cxxv, 99, and subsequent papers.

II. THE PROPHYLAXIS AND THE TREATMENT OF THE MILDER CASES OF NEPHRITIS

1. First of all it is necessary in any case of nephritis[1] to get as clear a conception as possible of all the factors which in our individual case conspire toward the production or the maintenance of an abnormal acid-content in the kidney. By doing this we are enabled to make a better attack upon our clinical problem. Rarely shall we find but one condition to be considered in the causation or in the maintenance of a nephritis. To the toxic cause of a scarlatinal nephritis may be added that of an inadequate lung ventilation if our patient develops a bronchopneumonia. To the toxic nephritis of a pneumococcus infection already aggravated by a decrease in available lung for respiratory purposes, may be added an additional item if the patient develops a convulsion and so (through muscular work) produces suddenly an enormous additional amount of acid. Our eclamptic patient that has just managed to drag through the last weeks of her pregnancy invites death when the additional acid production of the muscular efforts of labor or of a convulsion is added to that dependent upon the intoxication of her pregnancy. The patient with subacute or chronic nephritis, who, with persistent edema, some casts, albumin, and a deficient output of urine, is permitted or insists on working about the ward, may be keeping the camel's back broken with this added straw of acid production in even such light muscular work.

After we have removed as many of such conditions as possible, we may turn our attention to combating those which we cannot remove. These we must try to render as innocuous as possible. Directly or indirectly, we shall find ourselves face to face here with the necessity of fighting an intoxication. Not alone, as in an infectious disease, do we wish to keep the concentration of the unknown toxin produced as low as possible, for this is responsible for the abnormal production of acid in the cells of the kidney (and other

[1] The term nephritis is used throughout this paper in its ordinary *clinical* sense, as covering that symptom-complex which is characterized by the appearance of albumin and casts in the urine, by changes in the quantitative output of water and dissolved substances by the kidney, by the development of edema, etc.

organs) which we hold to be the direct cause of the nephritis, but this acid intoxication is itself a function of the concentration of the acid and this, too, do we wish to keep as low as possible. There is only one way to keep this concentration down and that is by giving water.

But the administration of water with intent to prevent or relieve a nephritis cannot be left to the haphazard desire of the patient. It must be insisted upon in a regular manner. A good rule is to give a glass every hour *day and night*. The night administration of water is as important as that through the day, for toxin production does not stop with nightfall, and if we ignore this fact we are likely to lose through the night what we may not be able to recover the following day, if at all.

As nephritis depends in the last analysis, according to our conceptions, upon an intoxication with acid, we try to avoid the effects of this upon the kidney (and other organs of the body) by giving with the water an alkali of some sort. Patients vary a good deal in this regard, but it may be stated as generally true that a continuous administration of alkali by mouth is not easily accomplished. This depends upon the fact that the pylorus does not open until free acid is present in the stomach,[1] and so alkaline solutions tend to remain in the stomach, to be vomited sooner or later.

The natural or artificial alkaline spring waters are perhaps most easily borne. If the patient will tolerate it, 0.5 to 1 gram of sodium carbonate or sodium bicarbonate may be added to each glass of these, or to plain water. Some patients who cannot tolerate the carbonates will take sodium citrate, sodium tartrate, sodium acetate, or other salts of a strong base with a weak acid in half-gram or larger doses every hour, either when dissolved in water or in capsules followed by water. Calcium hydroxide can easily be given by mixing lime water with milk. As the salts of the bivalent metals are particularly active in decreasing the hydration capacity of the body colloids, the administration of magnesium oxide or milk of magnesia up to the point where two or three easy move-

[1] W. B. Cannon, Jour. Amer. Med. Assoc., 1905, xliv, 15.

ments of the bowels are obtained daily, works very well. Also available in this regard are the soluble salts of calcium and strontium, as their iodides, acetates, citrates, or tartrates.

The dietary can be made an excellent and natural vehicle for getting alkali and salts into our threatened or established nephritic. A predominantly vegetable diet means a diet rich in alkali. It is hardly well to restrict the protein intake of our patient as greatly as has been our custom. It is better to allow a moderate protein ration on the condition that the patient will greatly increase his consumption of selected fruits and vegetables. It is well to bear in mind that vegetables and fruits will yield a greater proportion of alkaline and neutral salts when cooked than when raw. The sweet fruits, either raw or cooked, constitute a most agreeable form in which to get an excess of alkali over acid constituents into our patient.

For reasons that we have discussed many times before, we do not think that table salt should be restricted in a threatened or developed nephritic, but on the contrary should be urged upon the patient. Food serves as a natural carrier for this. In the form of salt meats and salt fish we can easily get considerable quantities of sodium chloride into our patient, and by placing a salt shaker at hand, he can liberally increase his intake by dusting it on his vegetables, his fats, and such proteins as we allow him.

Through the diet alone we can, therefore, do a great deal to keep the intake of alkali, salts, and water high.

2. Let us now imagine that in spite of these procedures our nephritic's symptoms do not improve. As we have already emphasized, many patients cannot long keep up a high consumption of alkali by mouth. The patient may begin to vomit the alkaline fluids we give him. Or "uremia" may begin in spite of our treatment, accompanied by vomiting, and we may again fail in our alkali therapy, even though the patient may be most willing to coöperate with us. Or let us imagine that the symptoms are rather severe from the start so that alkali by mouth seems inadequate. What are we then to do?

We continue to get as much use out of the gastric route as we can, but we now make use also of the rectum in order to get an absorption of water, alkali, and salt.

Before giving more specific instructions let us pause for another moment and consider once more just what we are trying to accomplish. We want to give the patient water. So far as this alone is concerned it matters little what form we choose. The reason we wish to give water is to assure ourselves that the general body colloids are saturated so that an excess remains to become available for urine. To accomplish this end alone, it would matter little whether we gave distilled water by rectum, or tap water, or any other available water.

In our every-day diet we never seriously consider whether our patient drinks distilled water, or tap water, or a table water. And from this point of view we might be inclined to ignore the exact composition of the liquid we inject into the rectum of our nephritic. But let us look at the problem a little more critically. The normal individual does not really with impunity ignore the matter of the form in which he consumes his water. It only seems so. In his food, the normal patient consumes large quantities of various salts, so that what he really consumes in any longer interval of time is a salt solution. The proper regulation of this—that is to say, the continuous consumption of a proper salt solution which in its turn maintains a proper salt concentration about the various cells in his body—is accomplished through the "taste" of the individual. If his salt consumption has been too high, he craves fresh water, and so washes out the excess of salts. If, on the other hand, he has lost too great an amount of salt from his tissues, he consumes more salt and makes up the deficit. The truth of these facts is attested by the most varied scientific and social facts. The animal treated with a strong salt solution makes desperate efforts to get at water, and the salt-starved animal licks the sides of its cage and laps up its urine to satisfy its demands for salt. The American retailer of beer feeds his customers salt meat and fish gratis. This gives them a thirst which they satisfy with beer, and overdrinking, they turn about and demand more salt food.

So when we give our nephritic water by rectum we must try to give him at least enough salt to cover also the washing-out effects that would follow if we gave the water pure. Therefore

the substitution of a "physiological" sodium chloride solution for the water, or better still a "Ringer" solution, is eminently in order.

But our nephritic has needs other than has a normal individual. We think that his kidney specifically and all the rest of his organs generally are suffering from an abnormal acid content. In consequence of this they have an increased attraction for water, and an increased capacity for holding water (an increased tendency to swell). We can decrease all this by neutralizing the acid with an alkali, and in proportion as we succeed in getting alkali into the circulation of our patient, we shall expect an improvement in all those signs and symptoms that are attributable to the increased water capacity of his body colloids. So we add alkali to the salt solution that we inject.

But we are not quite through yet in the determination of the exact composition of this rectal injection. The kidney in its capsule, the brain within the skull, the optic nerve in its foramen, tend in their swelling to press upon the vessels contained in them and so to aggravate the already precarious state in which the "nephritis" has placed them, by adding local circulatory disturbances that are in themselves capable of leading to an abnormal production of acid in the involved tissues. The increased colloidal swelling resulting from this complex of circumstances can be inhibited through salts. But to reduce the abnormal swelling a more than "physiological" concentration of salt is demanded. A "hypertonic" solution is necessary. To reduce the edema in the kidney or in the brain, in the optic nerve or in the tissues generally in our nephritic, we therefore try to increase, at least temporarily, the absolute concentration of salt in the whole body. We still further modify the solution by using a *hypertonic salt solution to which we have added an alkali.* Such a solution may be given by mouth, but it is better to give it by rectum, or, if necessary, intravenously. *Obviously when using such a hypertonic solution by rectum or intravenously we do not allow any water to be taken by mouth.* The patient may wet his mouth to relieve his sense of thirst, but no more, otherwise we would only be reducing the concentration of the solution we are administering by rectum. In

other words, we would not really be getting the increased salt concentration in the body tissues which we are seeking.

3. For practical purposes, now, what can we use? The following formula, or an even stronger one, works very well:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

Simple as is this formula, care must be taken in its preparation if good effects are expected. While we need not for rectal use insist upon the same grade of care that is necessary when such a solution is to be injected intravenously, it is well to consider everything even here.

Sodium *carbonate* is used, not bicarbonate. The carbonate is physiologically more effective than the bicarbonate, for one of the acids which are produced in the body is carbonic acid, and sodium bicarbonate is already saturated with this acid. In consequence, it cannot act as a carrier for this.

The chemically pure crystallized sodium carbonate ($Na_2CO_3.10H_2O$) or the monohydrated form ($Na_2CO_3.H_2O$) is to be insisted upon. Two other forms of sodium carbonate are found in the market, the dry (Na_2CO_3), and the so-called dry or "dried." The "dried" salt found on the ordinary drug shelf contains approximately two molecules of water of crystallization ($Na_2CO_3.2H_2O$). We are inclined to advise against all except the large crystallized form or the monohydrated form; but *whatever salt is used its water of crystallization content must be remembered, otherwise a solution of a different strength from that which we have found most useful will be obtained.* The proportionate amounts of these four salts that may be used are to each other as their molecular weights, or, in definite terms:

10.00 grams $Na_2CO_3.10H_2O$	(molecular weight 286)	crystallized "sal-soda"	=
4.95 grams $Na_2CO_3.2H_2O$	(molecular weight 142)	"dried"	=
4.33 grams $Na_2CO_3.H_2O$	(molecular weight 124)	"monohydrated"	=
3.71 grams Na_2CO_3	(molecular weight 106)	really "dry"	

The sodium chloride-sodium carbonate solution should be made up in *distilled* water and filtered. If the salts used are pure and

the whole is properly prepared the resulting solution is perfectly clear.

Rectal Injection of the Solution. Unless our patient is mentally incapable of comprehending what we have to say, it is well to explain to him before an injection is made just what we desire to accomplish and so secure his coöperation. As the solution is hypertonic and contains alkali in addition, it not only irritates the rectum somewhat but leads temporarily to a secretion of water into the rectum while the salt and alkali are being absorbed.[1] The patient, in consequence, has a desire to go to stool, which after we have once permitted him to satisfy, we wish him to overcome. By obtaining his coöperation, the solution is retained for longer periods of time, or entirely, and correspondingly we get a more perfect absorption of the alkali and salt.

To inject the solution we may make use either of a continuous drip method, or inject larger quantities at varying intervals of time. It is not necessary to first cleanse the rectum locally, and especially are we *not* to try to accomplish this end by a previous administration of cathartics. Both these methods only increase the irritability of the rectum, so favoring expulsion of what we inject. It is well, of course, if the lower bowel is empty (as immediately after the patient has had a stool). But if no movement has occurred recently we make our injection just the same. Perhaps the patient will then have a stool from the alkali-salt solution injected. This cleans the rectum, and we begin again.

For administration of the alkali-salt solution the patient should first be comfortably arranged in bed. He should lie on his left side on a rather hard bed and with no pillow, or only a small one, under his head. His hips may be elevated slightly to give still greater pitch to the rectum, but this should not be attempted unless the patient can be made *perfectly* comfortable.

We are now ready to inject the solution, and may choose either the slow *drip method* or the *fractional instillation* method. The

[1] No solution is absorbed or secreted "as such," as is usually taught. See Martin H. Fischer, Edema, 200, New York, 1910; Kolloidchem. Beihefte, 1911, ii, 304; available in English in Cincinnati Lancet-Clinic, 1912, cvii; Nephritis, 113, New York, 1912; James J. Hogan and Martin H. Fischer, Kolloidchem. Beihefte, 1912, iii, 385.

choice from the patient's point of view is about evenly divided between the two, and he should be consulted and his wish followed.

The *fractional instillation* method will be described first. For this the apparatus shown in Fig. 1 may be used. *A* is a funnel that has a capacity of not less than 250 c.c. *B* is a soft rubber tube at the lower end of which is the pinch clamp *C*. *D* is a short glass tube that connects *B* with the soft rubber catheter or rectal tube *E*. The solution to be injected is heated to 40° C., and the patient being in position, the catheter is lubricated with vaseline. Into the funnel are now poured 250 c.c. of the solution, and the stop-cock is temporarily opened so as to drive the air out of the tube and catheter. The catheter is then gently inserted well into the rectum and the funnel is emptied by again opening the pinch-cock. The short glass tube will inform the operator when the last portions of the mixture are flowing into the rectum, when the hold on the pinch-cock is released. In this way no air will be allowed to enter the rectum and balloon it, and extra irritation from this source will be avoided. If the patient's lower bowel has been empty, the injection is usually easily retained, and may be repeated in half or three quarters of an hour. If the bowel was filled with fecal matter the first injection serves to bring on a movement, and the cleared bowel will subsequently absorb better. The injections may be repeated as often as the symptoms of the patient demand it, or until the patient finds them difficult or impossible to retain. A period of rest should then be given. If our case is so urgent that this cannot be allowed with safety, then the solution must be given intravenously (see below).

When we wish to give the solution by a *continuous drip method* the arrangement shown in Fig. 2 works very well. *A* is an ordinary half liter or liter graduated irrigating vessel with a side tubulation. It connects through the rubber tube *B*, carrying a pinch-cock *C*, with the glass insert *D*, in which lies a thermometer. The insert connects with the soft rubber catheter or rectal tube *E*. *F* is a glass insert which permits us to observe the rate at which our solution is dripping into the rectum. From 1 to 4 drops a second should enter the rectum. This is about as high a rate of injection as the patient can stand without rejecting the fluid. Roughly,

this corresponds to an injection of from 240 c.c. to 960 c.c. per hour.

The injection fluid is retained best if it is delivered *into the patient* at not less than body temperature, and 40° C. is better. For this reason the thermometer in *D*, located as near the rectum as possible, is of great convenience. As the solution slowly passes out of *A* through the tube, it falls in temperature. The vessel *A* is therefore

Fig. 1

Fig. 2

conveniently filled with the solution at a temperature somewhat above 40° C. Or one can set this vessel into a second one containing warm water, or place the tube *B* in warm water, or cover it with a blanket by way of maintaining the solution at a proper temperature as convenience and the ingenuity of the medical man dictate.

In hospital practice, thermostatic devices heated by electricity or gas may be installed conveniently.

4. How much of the solution may be given by rectum and how long do we continue with it? The answer to this is found in the condition of the patient. So far as I have been able to observe, no harm can be done by indefinite use of the solution. *A full physiological effect is obtained when the patient is kept free from the various signs and symptoms of nephritis, and the urine is persistently neutral in reaction toward litmus.* Such a full effect may be obtained in a day or two, or it may require a week. The symptoms may have cleared entirely even before the saturation of the body with alkali has been carried to the point where the patient secretes a persistently neutral urine. His improvement will by itself suggest a reduction in the number of injections or their entire abandonment.

Individuals differ greatly in their behavior toward these injections. I have seen patients bear them for weeks at a time without complaining, and without ever rejecting them. Others will insist from the first that they cannot hold them. In this connection it is well to point out that if these hypertonic salt-alkali mixtures are retained for any time at all, say even for an hour, they do much good. When at the end of such a period the patient rejects some fluid from the bowel, this is not the same as that which we introduced, simply minus a certain quantity that has been absorbed. Hypertonic sodium chloride-sodium carbonate mixtures are not absorbed as such. The salt and alkali are absorbed out of the solutions while water is being secreted into the bowel. Therefore, if the solution is retained even for a short time, the patient will have increased his body-content of alkali and salt, which is the whole purpose of our therapy.

It is well, if possible, in the first twenty-four hours of treatment to have two liters of the solution retained by the patient. For a few hours after starting the injection it is well to give him but little water by mouth, for we wish to have as great a shrinking effect upon all the tissues (including the kidney) of the body as possible. But as soon as we see the urinary output begin to increase and rise toward a more normal point, we urge the patient to drink water, so as to have free water available for urine. While initially we can and wish to get this by robbing the patient's tissues of water (reducing his edema), there is a limit to the amount that

can thus be obtained, and we must then furnish water from the outside. I find some practitioners overlooking the importance of this point constantly. While some water is introduced with the hypertonic salt solution, most of the "free" water that is lost through the kidney after absorption of the hypertonic solution has been taken from the tissues (which may be edematous). But it is self-evident that this robbing of the tissues can only go on for a limited time. Then we have to supply water from the outside if we wish to keep up the urinary secretion. The thirst developed by the patient when treated as here suggested with alkaline hypertonic salt solution helps us in this regard, and we are glad to satisfy it as soon as we find that his kidneys are better able to secrete water.

If for any reason (as when the patient is comatose or vomiting) we cannot feed enough water by mouth, then we can use the rectum. After we have gotten our kidneys functionating in a more normal way by the use of hypertonic sodium chloride solution containing sodium carbonate we may substitute for it a solution more nearly isotonic with the body fluids. A "physiological" salt solution (0.85 per cent. to 0.9 per cent. NaCl) does very well, though the following mixture is to my mind better, for it gives the much needed alkali as well as the necessary water.

Sodium carbonate ($Na_2CO_3.10\ H_2O$)	10 grams
Sodium chloride	7 grams
Water	1000 c.c.

This solution may be injected in indefinite amounts, and gives rise to no rectal irritation. But since it is not hypertonic, it does not produce as marked or as rapid general effects as we seek in the more acute manifestations of nephritis.

The desire to introduce into our nephritic the bivalent metals which would dehydrate his body colloids far more than do the univalent metals that we use, cannot be easily satisfied. The reason for this is obvious. Their hydroxides are largely insoluble, and so the administration of bivalent metals such as calcium or magnesium along with carbonates or hydroxides is impossible. The only schemes that I have found of service are limited to cases

of mild nephritis and to such as are recovering from the severer types, where lime water may be added to the milk consumed by the individual, or he be given magnesium oxide, milk of magnesia, and soluble calcium or strontium salts by mouth. For rectal injection a "physiological," 0.85 per cent. sodium chloride solution, to which 0.1 per cent. calcium chloride is added, also works very well if alkaline solutions have not been used for some hours previously.

III. THE TREATMENT OF SEVERE CASES OF NEPHRITIS

1. Under this heading we shall consider those patients in whom we encounter such especially alarming signs and symptoms as great or complete suppression of urine, rapidly progressing optic-nerve changes, persistent headache and nausea, vomiting, convulsions, stupor and coma, great quantities of albumin in the urine, etc.

While we realize that a complete explanation of the nature and of the cause of these various clinical signs cannot be summed up in any brief statement, we believe that an essential, if not the essential element in all of them is an edema of the affected part. This edema is represented physicochemically by an increased swelling on the part of the colloids of the tissues involved, and as responsible for such an increased swelling, we hold the abnormal production or accumulation of acid in the part, either alone or in conjunction with such other substances as are also capable of increasing the hydration capacity of the tissue colloids. Or, to repeat what we have already emphasized numerous times before, *what we call the serious complications of nephritis are not really complications secondary to this pathological entity, but are manifestations in other organs of the body, of the thing which in the kidney we call nephritis.*

Just as the nephritis is in large measure an edema of the kidney, so the optic nerve swelling and the "retinitis" of nephritis are edema of the optic nerve and of the retina; the headache, convulsions, and coma are manifestations from an edema of the brain the persistent nausea and vomiting of central origin, manifesta-

tions from an edema of the medulla; the generalized edema, an expression in the body tissues of what in the kidney we call nephritis. The same intoxication underlies all these changes, and it is a mere accident, not immediately analyzable, that one nephritic will show particularly prominent eye symptoms, another a great generalized edema, while a third will call us to his side by a convulsion. For anyone of a number of reasons, the edema may become particularly prominent in his optic apparatus, or in his body tissues generally, or in his brain. If we bear these facts in mind, it will serve to indicate why we believe that any or all of these signs demand the same general treatment, and why, if we succeed in combating a particularly prominent one, we find that we have succeeded in combating all the rest as well.

Whether the particularly alarming symptoms spring from the kidney itself (a suppression or urine, a great albuminuria, etc.), or whether they spring from the brain (convulsions, stupor, coma), the eye ("papillitis," "retinitis," partial blindness), or the medulla (nausea and vomiting), the purpose of our therapy is the same —we wish to stop and reduce the swelling of the involved tissues.

Naturally the best and quickest way to do this is to inject something into the blood, and what this something must be we have already discussed. We wish to neutralize the acids that are present in abnormal amounts in the involved tissues; we wish to decrease the hydration capacity of the tissues by increasing their salt content; we wish to have the body tissues saturated with water and some left over to be available for secretion as urine. The quickest way to do all this is to inject intravenously a hypertonic sodium chloride solution to which we have added sodium carbonate.

2. The following formula, already recommended above, does very well:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

It is well to have this solution ready for immediate use, for its preparation in sterile form takes time, and need for it when it arises is urgent. What we have said already regarding chemicals holds here also. Only chemically pure salts and *freshly distilled*

water are to be used. The crystallized sodium carbonate containing ten molecules of water of crystallization is recommended. If some other form of the salt is used, less than 10 grams to the liter are to be used, as discussed above.

The finished solution as injected into the patient must be perfectly clear and sterile. Simple as it would seem to be to obtain this result, it is not always secured even when its preparation is left to trained helpers. Therefore, I may be pardoned for detailing the following rules for its preparation in containers that make it available for immediate use.

Trouble arises from the fact that alkaline solutions cannot long be kept in contact with ordinary glass containers without reacting with the glass and so leading to a separation of insoluble silicates. Jena glass flasks resist better than other material, and so the finished solution may be sterilized and kept in these. For this purpose, it is only necessary to dissolve the sodium chloride and the sodium carbonate in the necessary amount of freshly distilled water and filter the solution through moistened filter paper (in order to get no shreds into the solution) into thoroughly cleaned Jena flasks which have been rinsed in distilled water. It is convenient to have two liters of solution in each flask. The flasks are stoppered with gauze-wrapped cotton stoppers, and may be sterilized in the ordinary way by boiling. This scheme works well in hospitals or anywhere where storage room is plentiful.

When needed for injection, this solution may then be poured into any one of the properly sterilized intravenous injection apparatuses that abound in the market. If the solutions show a precipitate in spite of the use of Jena glass containers, the clear solution may be decanted or the whole may be filtered through a sterilized funnel into the neck of which has been forced a little sterile glass wool. Or a sterilized glass bulb insert of the type shown in Fig. 3, into which has been forced some glass wool may be used in the delivery tube of the injection apparatus. As the carbonates and hydroxides of the polyvalent metals are all insoluble, every piece of any injection apparatus must be rinsed and sterilized only in *distilled water*. When ordinary tap water is used calcium and magnesium precipitates cloud the injection mixture.

For myself I have found it best to make up the sodium chloride-sodium carbonate solution in ampoules, and then mix this concentrated solution with enough freshly distilled water to yield the proper injection mixture at the time this is needed. One proceeds as follows:

Fig. 3

Any desired number of multiples of 10 grams of sodium carbonate ($Na_2CO_3.10H_2O$) and 14 grams of sodium chloride are dissolved in enough water to make 60 c.c. of finished solution. This solution is filtered and then sterilized by boiling.[1] One or more ampoules of the type shown in Fig. 4, *A*, and of about 60 c.c. capacity (if these are not available, bottles will do as well) are

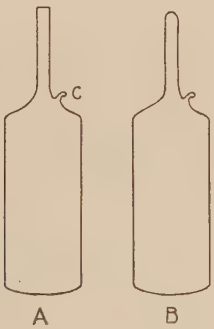

Fig. 4

thoroughly cleaned, rinsed in distilled water, and then boiled in distilled water to sterilize them. Into each of these is then filtered through a small sterilized funnel plugged with glass wool, 60 c.c. of the concentrated sodium carbonate-sodium chloride mixture. When the ampoules have been filled, they are sealed in a flame, as in Fig. 4, *B*. If bottles are used they are corked with sterile corks,

[1] In my book on nephritis and in a paper or two I have cautioned against the use of excessive heat in sterilizing these carbonate solutions. The caution I find was scarcely necessary, for at the ordinary temperatures and pressures at which such sterilization is carried out, the carbonate is not decomposed.

and over these is fastened a sterilized paper hood to protect the necks from contamination. When an intravenous injection is to be given, an ampoule is taken, its neck is nicked with a file, and this and the lateral bead are cleaned with alcohol, and broken off. The contents are then poured into 940 c.c. of freshly distilled water, *care being taken to mix the whole* so that the specifically heavier salt solution may not simply settle to the bottom.

After many trials I have found these the best ways to proceed, and as dispensing pharmacists in any community are willing to carry ampoules as here described in stock, one can easily obtain fresh and clean solutions at all times. If a precipitate of silicates should be found in an ampoule, one can readily avoid pouring this into the injection apparatus, or one may filter the contents of the ampoule through a little glass wool.

The Intravenous Injection of the Solution. The experience of the last year has convinced me that it is best in making these intravenous injections to cut through the skin and expose the vein to be used clearly to view. The results are bad if one fails in his attempt to enter a vein with a hypodermic needle through the skin. The salt-alkali mixture produces a great destruction of the tissues if it is by accident injected into them.

A vein that is deemed sufficiently large is sought in the arm, in the leg, or, if necessary, in the neck. As we may wish to make several injections it is advisable to pick for the first injections the prominent veins *most distant* from the heart. Unfortunately in many of the conditions in which we wish to use the sodium chloride-sodium carbonate solution, not much choice is allowed us, for the bloodvessels are so much contracted (toxemic shock?) that it is often impossible to find any usable vein below the bend of the elbow. Even here surgeons have been unable to find the median basilic in such cases. This will explain to the reader why in extreme cases such a vein as the jugular needs to be and has been used.

To expose the vein painlessly a few drops of a cocaine or a novocaine solution may be injected into the skin. If the patient is stuporous or in coma this is, of course, needless. The vein is freed from its surroundings and a ligature is tied about its distal end. A second ligature is thrown about the vein and after a cut has been

made into the vein and the cannula connected with the injecting apparatus has been inserted, this second ligature is tied. Care is, of course, taken to have no air enter the vein.

The best type of cannula to use is shown in Fig. 5. The two openings at the tip and laterally make it well-nigh impossible to shut off the infusion stream by crowding the cannula against the vein wall. The tapering character of the cannula allows one to push it into even a small calibered vein, and the corrugation holds the cannula in place when the second ligature is tied.

Fig. 5

Sometimes it is better to use a large hypodermic needle in place of the cannula. The first ligature about the exposed vein then serves to steady the vein when the needle is pushed into it. When the hypodermic needle is used it is simply held in place until the injection is completed. As can easily be imagined, the use of the needle is especially convenient if one works with such a vein as the jugular. The disadvantages in its use arise from the fact that one is likely at any time to injure the bloodvessel if the patient moves, and from the further fact that the carbonate solution affects the coat of the vein and so tends to leak out about the needle after the injection has been kept up for some time.

As we have already mentioned, any of the various apparatuse on the market for intravenous injection may be used to give the alkaline hypertonic sodium chloride solution intravenously. The medical attendant should choose the apparatus with which he is most familiar.

Perhaps that shown in Fig. 2, with a cannula replacing the catheter, and minus the thermometer and the insert *F* is the simplest available form. The side tubulation with the rounded bottom or a glass bulb insert filled with glass wool (Fig. 3) will make it almost impossible, if care is used, to inject any sediment that may accidently appear in the injection fluid. *The rate of inflow must be slow* and is conveniently regulated by gravity.

The pressure bottle arrangement shown in Fig. 6 possesses some advantages over the apparatus just referred to. No special comment is necessary regarding its use, and we need not in this day emphasize the necessity of having all rubber tubes, etc., perfectly sterilized by boiling in distilled water.

The faults of the apparatus shown in Fig. 6 are that it possesses no arrangement for keeping the solution at body temperature, and that we do not know in as accurate a manner as we desire, the

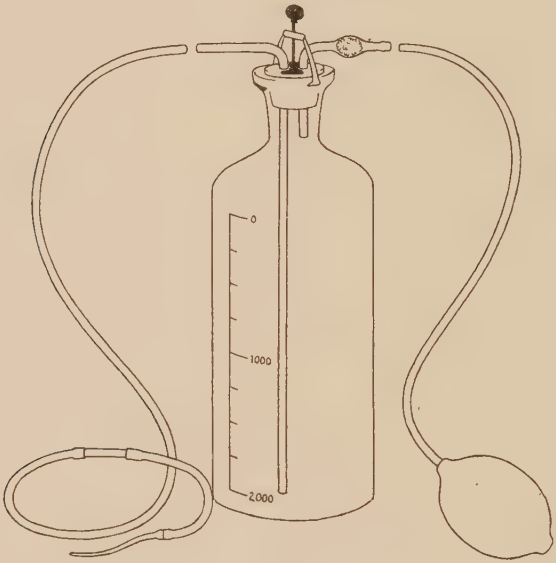

FIG. 6

exact rate and the exact pressure at which the sodium chloride sodium carbonate solution is entering our patient at any moment. To meet these difficulties, the very useful apparatus shown in Fig. 7 was devised by Edmund M. Baehr. We have here again the same glass pressure bottle already shown in Fig. 6, but this is surrounded by a copper water jacket by means of which the injected fluid may be kept at body temperature or a little above. The thermometer registers the temperature existing in the jacket, and as the temperature of the injection fluid falls on its way into the

patient, it is advantageously kept 3° to 5° above the temperature at which we wish to deliver the solution into the patient. The rubber bulb shown in Fig. 6 is advantageously replaced in the apparatus shown in Fig. 7 by a metallic pump, and a mercury manometer inserted as indicated in the drawing, allows one to know at all times the exact pressure obtaining in the pressure bottle.

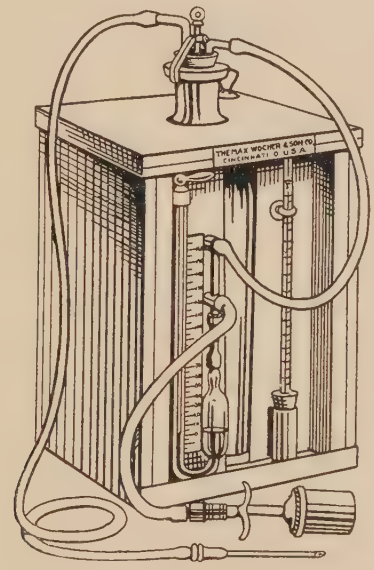

Fig. 7

One needs at all times to inject the solution slowly into the circulation so that it may mix with the blood, and at as even a rate as possible. Not over 30 to 40 c.c. should be injected per minute. By testing out the apparatus before making the injection one can easily note just how much pressure is necessary to accomplish this. As the pressure in the larger veins is almost *nil*, 30 to 40 mm. of mercury pressure usually suffice, and one need never run above 50 mm. if a cannula or needle of proper diameter is chosen. If we give the solution to a patient who for any reason has to maintain an upright position, it is well to remember that in such a case the arm must be comfortably supported in as horizontal a position

as possible in order not to have to work against a considerable hydrostatic pressure in the veins. The pressure and the oscillations of the mercury column tell us every moment whether our solution is flowing in properly or not.

3. We need to say now how much of the solution may be injected at any one time and how often we may repeat the injection.

In any suppression case or in a case with convulsions, persistent vomiting or other alarming symptoms, 1800 to 2000 c.c. of the solution should be given for the first dose. In the case of a child we give a proportionate dose obtained by dividing the child's weight by that of a small adult. A 30-kilo child gets half the dose of a 60 kilo man, etc. The repetition of the injection and the amount given subsequently must then be determined by the condition of the patient. If, within two or three hours, urine begins to come and the convulsions stop, or if the sensorium clears or the headache and eye symptoms improve, then we know that we have given enough for the time being.

If the patient is mentally awake, he is likely to complain of thirst during the hour that we are making the injection. We do not immediately let him satisfy his thirst, for we wish to get as great a shrinking effect of the salt and alkali upon his various organs as possible. But there is no objection to his moistening his mouth, and at the end of two or three hours, if his alarming symptoms seem to be under control, we are only too glad to have him drink, for we must have all his tissues saturated with water before we get "free" water available for urine. Only we must always remember that as soon as water is given we decrease the patient's salt concentration, and if his kidneys are functioning, we are actively washing salt out of the body. So, to carry along our therapy, we give a natural or artificial alkaline water instead of plain water by mouth, and with this we may give various salts. By thus giving alkali and salts by mouth or by using alkali and salt by rectum, we may now be able to keep our patient growing progressively better. But if this is not the case, or if the redevelopment of some prominent sign or symptom informs us that our patient is relapsing into his previous state, then we may give a second injection of one or even two liters of solution, six, twelve,

or twenty-four hours after the first injection. Closer rules than this can hardly be given. If our patient improves for a number of hours after the first injection, and then goes down again, we repeat the injection at this time; 500 to 1500 c.c. in any twenty-four hours after the first injection is certainly safe.

If the supposition of urine is not absolute, then we have in it a useful guide as to the amount of alkali and salt therapy that we may urge upon our patient. It is safe to give this, and it should be given until the urine is *persistently* neutral to litmus. For self-evident reasons, it is possible for the urine to be alkaline immediately after an intravenous injection, even when the acid content of the body generally is still abnormally high. Not until the urine is *persistently* neutral can we therefore say that we have really succeeded in getting an adequate amount of alkali into our patient.

Perhaps the way to proceed can best be illustrated by the abstracts of a few clinical cases and some direct comment upon them.

IV. CLINICAL ABSTRACTS AND COMMENT

Case I.—Mr. G. B., a laborer, aged twenty-four years, and previously in good general health, was operated upon under ether at 9 P.M. February 15, 1912, for a right inguinal hernia of several years' standing. The operation was a long one. Examination of the urine before operation had been negative. Nothing abnormal was noted except that vomiting was rather severe after the operation, continuing until late in the afternoon. At this time, in response to inquiry the patient said he had no desire to urinate. The same condition existed late that night, even though by this time the patient was swallowing and retaining considerable quantities of water. The following morning the patient was catheterized, and 20 c.c. of brownish viscid liquid heavily loaded with albumin were obtained. Through the day he was given hot drinks and hot fomentations over the kidneys, but no spontaneous voiding occurred. At 9 P.M., that is to say, eighteen hours after the operation, he was again catheterized, and 15 c.c. of urine of the previously described character were found. At the same time liquid by mouth was stopped and administration of the following solution by slow drip into the rectum was started:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

The patient retained the solution well, and by 10.30 had taken up the whole liter. At 11.45 he asked for a urinal, and passed 180 c.c. of highly albuminous urine filled with casts and red blood cells. At 1 A.M. he passed another 160 c.c., and at 3 A.M. 205 c.c. The urine by this time was almost as clear as water.

As he felt thirsty, a glass of water was now permitted him every hour. The urinary output continued so that by 9 P.M. of February 16, that is to say, in the first twenty-four hours after the drip was started, 2350 c.c. were voided. By the evening of this day the albumin had dwindled to a trace, and only occasional granular casts could be found.

In the following two days, during which 2470 and 2385 c.c. respectively of urine were obtained, these signs disappeared entirely. The urine of this patient, who is entirely well, has been examined repeatedly since, with negative results.

CASE II.—Mrs. M. L. T., aged forty-seven years, a laundress, was operated upon under ether for an extensively broken pelvic floor with prolapse of the uterus, at 8.30 A.M., July 1. She had not been in good general health previously, though she complained of nothing specifically except her uterine condition. Urinary examination on admittance to the hospital the day previously had shown a trace of albumin and occasional casts, but the general condition of the patient did not seem sufficiently bad to contraindicate an operation which was much needed. The patient's condition after the operation was fair, but she did not urinate. Catheterization twelve, twenty, and twenty-eight hours after her return from the operating room was dry. At 9 P.M. July 2, when catheterization was again found to be dry, she was slowly injected intravenously with 1600 c.c. of the following mixture:

Sodium carbonate ($Na_2CO_3.10H_2O$)	20 grams
Sodium chloride	28 grams
Distilled water enough to make	2000 c.c.

She was catheterized at 3 A.M., when 90 c.c. of a viscid, brownish urine, filled with albumin and casts, were obtained. The urine was highly acid to methyl red.[1] At 7 A.M. another 90 c.c. of a similar looking urine were obtained. Because of the perineal operation, rectal injection of alkali and salt was not urged, but half a glass of Vichy water, with a powder of half a gram each of sodium bicarbonate and magnesium oxide, was given every hour. On this regime 420 c.c. in all of brownish, highly albuminous urine filled with casts were obtained in the first twenty-four hours after

[1] Methyl red and paranitrophenol are indicators that are less sensitive to acids than litmus. Reaction with these indicates an abnormally high acid content in the urine. Their use clinically will be discussed in a forthcoming paper.

the intravenous injection. This alkali therapy was continued. The urine became neutral to litmus and remained so after July 5. In her second twenty-four hour period she secreted 670 c.c. of urine, and in the third, 1140. The urine became clearer, the casts fewer, and the albumin content diminished steadily (from 9 grams to the liter in the first specimens to 1.5 grams on July 5 and 6). Her further history is summarized below:

For 24-hour period of	Amount of urine.	Grams of albumin per liter (Esbach).
July 7	1790	1.0
July 8	2100	0.8
July 9	1873	0.9
July 10	1840	0.5

Numerous hyaline and granular casts were found in all these specimens. These continued with a urinary output of 1700 to 2200 c.c. per twenty-four hours, containing albumin that varied little from half a gram per liter until she was discharged from the hospital July 21.

A more detailed physical examination after her operation than had previously been possible, showed this patient to have easily palpable peripheral bloodvessels with an evidently enlarged but regularly beating heart. The systolic blood pressure was 165 mm. of mercury, the diastolic, 140. Tender bones with bogginess of the tibial periosteum, a tender nasal bridge, vague night pains, and three miscarriages for which no cause was assigned, together with the casts and albumin found on admission to the hospital, led to the diagnosis of syphilitic vascular disease with cardiac hypertrophy and involvement of the kidney (chronic interstitial nephritis).

Since leaving the hospital this patient has been seen occasionally. Some albumin and casts are constantly found in the urine, and her blood pressure continues at approximately 160 mm. The patient herself complains of nothing and feels herself improved by her operation.

In the light of our consideration in the early paragraphs of this paper, it cannot surprise anyone to find that an anesthesia nephritis as illustrated in these two cases is easily relieved when alkali and salt are introduced into the body. During an anesthesia we introduce into the body a poison which interferes with the normal oxidation chemistry in nearly all the cells of the body, and that we have an abnormal production and accumulation of acid in the body following this, is attested to not only by the thirst of which the patient complains, but by the accelerated breathing and heart beat, the abnormally high acid (hydrogen ion) content of post-anesthetic urine, and the appearance in it of

such "acidosis" products as acetone, diacetic acid, lactic acid, etc. But as soon as we stop administering the anesthetic the patient begins to exhale this, and so in a comparatively short time the intoxication responsible for the abnormal production and accumulation of acid in his body disappears.

The patient also usually succeeds in oxidizing the acid products resulting from his intoxication, and so it is the usual thing to see a patient bear his anesthesia without bad after-effects. But sometimes he is not so successful in overcoming the effects of his anesthesia and then if his intoxication evidences itself chiefly from the side of his kidneys, we say he has a postoperative nephritis. (If it should happen to involve his liver particularly, we say he has a "postoperative jaundice," "chloroform liver," etc.). Very evidently there is nothing surprising about the fact that an administration of alkali and salt relieves this condition. The alkali neutralizes the abnormal acids present, and the increased salt concentration reduces the hydration capacity of his swollen kidney (and other body) colloids. If the injury to them has not been too great (or technically put, if the colloidal change that is characteristic of nephritis has not become "irreversible"), these measures therefore quickly restore his kidneys (and other involved organs) to a more normal state. As the kidney shrinks, a better blood supply to this organ is obtained, and so the kidney cells themselves are also once more enabled to resume their work. Once we have obtained this result a recurrence need scarcely be feared, for the original intoxicant (the anesthetic) has by this time disappeared from the body, and so the relief obtained is permanent.

What we have just said applies in my judgment to Case I. In Case II the problem is essentially the same, only the anesthesia intoxication is this time added to the effects of a bloodvessel disease which in itself has already led to the signs of a nephritis. The effects of the anesthesia intoxication could, as in Case I, be overcome, but an injection of salt and alkali does not remove an endomesarteritis with its effects upon the kidney, and so casts, albumin, etc., continue to be found in the urine even after the suppression following the anesthesia has been relieved.

If we will write the name of any other intoxicant in the place

of anesthetic in these considerations, we have what happens, to my mind, in the nephritides that we encounter in any of the acute infections, and in the various other acute intoxications which we know to be associated with the development of nephritis. Here again nature herself takes care of the great majority of cases, but when she does not, we may again be able to relieve the urinary condition by alkali, salts, and water. Such a situation is illustrated in Case III, where an unknown intoxicant led to suppression of urine.

Case III.—(Dr. Elizabeth Campbell, Cincinnati, Ohio.) A. H., a girl, aged three and one-half years, had never been ill previously. When first seen she was extremely nauseated and vomiting. There was a slight general edema, and her urinary output was low. The urine contained much albumin and casts. Enemas of 0.85 per cent. sodium chloride solution and calomel by mouth improved the child's condition, and brought up the urinary output. Five days later the mother reported that since two in the afternoon of the day before the child had passed no urine. The child was given hot baths and sweated several times. Several 0.3-gram doses of sodium bicarbonate were given by mouth, and water was urged. The child had vomited once. She was extremely quiet. Temperature and respiration were normal. The pulse was 76. 0.2 gram calomel was given at night, and through the night hot alkaline drinks, blanket sweats, and enemas of 0.85 per cent. sodium chloride solution were continued. The anuria persisted. This scheme of treatment was kept up through the following day also. The general edema had in the meantime increased, the patient was vomiting, and had grown stuporous, and the pupils reacted slowly. In consultation in the early evening of this the third day of the anuria it was decided to try the administration of an alkaline hypertonic sodium chloride solution. As it was thought there might be some urine in the bladder, the child was catheterized. A teaspoonful of bloody urine was obtained. At 9 P.M. 320 c.c. of the following solution were injected into the rectum by slow drip, the child retaining all of it.

Sodium carbonate ($Na_2CO_3.10H_2O$)	15 grams
Sodium chloride	14 grams
Water, enough to make	1000 c.c.

The child had a restless night. At 5 A.M. she passed 96 c.c. of urine that looked like pure blood. This was sixty-three hours after the suppression was first noted. At 6.15 A.M. another 130 c.c. of bloody urine were passed; at 7.30, 256 c.c., with only a slight amount of blood. At 10 A.M. a large

voiding was lost with a watery stool. An hour later 250 c.c. of the above alkaline hypertonic sodium chloride solution were slowly injected into the rectum. Through the afternoon the nurse reported that "the urine came in an almost steady stream." The albumin content of the urine fell rapidly, so that by the following day only a trace could be found, and on the fourth day later it disappeared entirely. The general edema disappeared rapidly, and was about gone on the third day after the urinary secretion became reëstablished. Recovery has been complete.

For self-evident reasons our prognosis grows worse and our efforts need to be greater as the intoxication grows in length or becomes of a less removable type. We encounter this situation in protracted infections, in acute infections that leave behind toxines that stick particularly firmly to the kidney cells (scarlet fever?) and in poisonings of this type (phosphorus and the metals). Not alone do some of these produce irreversible colloidal changes (necrosis) in the cells of the kidney from the start—changes, therefore, which can never be "cured" by any therapeutic procedure—but even when such is not the case, in these lasting intoxications the interference with the normal oxidation chemistry of the kidney cells is of a more lasting character, and so our therapy must also be more persistent. And so in the nephritides following mercury or arsenic administrations, in those accompanying acute and chronic infections, in those of pregnant women, a single dose of alkali and salt may do no more than give temporary relief. We must meet the intoxication as long as it persists, and only as the nature of the intoxication permits of this, or our skill is equal to the occasion can we hope for good results.

Cases IV, V, VI, and VII may serve in illustration of some of these remarks.

Case IV.—(Dr. C. C. Fihe, Cincinnati, Ohio.) Mrs. E. J. H., aged twenty-six years, showed much albumin and many casts in her urine, and developed a generalized edema in the seventh month of this her first pregnancy. Her urinary output was scanty and highly colored, and she felt herself below par. Her physical activities were much restricted, and she was placed on an active alkali therapy. Vegetables and sweet fruits were urged upon her, sodium phosphate and citrate were frequently given, and at regular intervals sodium carbonate and sodium chloride were

administered in capsules followed by water. Her symptoms cleared markedly, and she was carried to term, voiding 700 to 1500 c.c. of urine daily.

At midnight, February 1, she went into labor, and at 8.30 A.M. was delivered of a living child. She had passed no urine the day previously, and none was passed during these hours. A gradually increasing blurred vision in her right eye, of which the patient had complained for several days past, had increased. She complained of headache. At 11 A.M. a convulsion lasting ten minutes occurred, and at 2.30 P.M. another lasting twenty minutes. At both times chloroform was administered. She was catheterized and 30 c.c. of dark brown urine filled with albumin were obtained. At 5 catheterization was dry. The pulse ranged between 148 and 92. At this time 150 c.c. of the following solution were given intravenously:

Sodium chloride	14 grams
Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Water, enough to make	1000 c.c.

A severe convulsion occurred while the intravenous injection was being made, and so this had to be discontinued. 0.015 gram morphine was given hypodermically, and another 250 c.c. of the solution were injected into the rectum. At 8.15 P.M. 1200 c.c. of urine were obtained by catheter from the bladder. At 8.45, 1200 c.c. of the above solution were given intravenously. An unmeasured amount of urine was passed with a stool at 10.30. At 11, 1022 c.c.; at 12.30, 96 c.c.; at 2.40, 16 c.c.; at 6.40, 512 c.c. were passed voluntarily. The pulse gradually fell during these hours to 76. Sodium phosphate, sodium carbonate, and sodium chloride were given in small doses at regular intervals by mouth, and after the first signs of a freer urinary output, water and milk were urged at hourly intervals. In the first twenty-four hours after the intravenous use of the alkaline hypertonic salt solution, 4814 c.c. of urine were passed, not counting two voidings that were lost. The patient's uneventful subsequent history is summarized below. Five grams each, per twenty-four hours, of sodium chloride and sodium carbonate were given in divided doses in capsules followed by water, at regular intervals day and night. In addition, 15 grams of disodium phosphate were given once or twice daily, and for the patient's anemia, 0.5 c.c. tincture of iron chloride three times daily was prescribed.

Date.	Temperature.	Pulse	Urine in 24 hours.	Albumin in grams per liter (Esbach).	Remarks.
Feb. 2– 3	98.0° to 98.6°	78 to 80	4128+	1.0	Milk diet
Feb. 3– 4	98.2° to 98.6°	68 to 78	5578	0.5	Milk diet
Feb. 4– 5	98.2° to 98.6°	64 to 74	4127	0.5+	Light mixed diet
Feb. 5– 6	98.2° to 99.2°	72 to 86	5382	0.5	Light mixed diet
Feb. 6– 7	99.0° to 100.2°	74 to 86	4288	0.5—	Light mixed diet
Feb. 7– 8	98.6° to 99.6°	74 to 80	3904	0.25	Light mixed diet
Feb. 8– 9	98.0° to 98.6°	68 to 75	5272	Trace	Light mixed diet
Feb. 9–10	98.6° to 99.0°	68 to 72	4032	Trace	Light mixed diet
Feb. 10–11	99.8° to 98.0°	70 to 72	2200+	Trace?	Light mixed diet
Thereafter until March 10	Normal	Normal	1700 to 2700	No albumin	No dietary restrictions

Case V.—(Dr. W. A. Clark, Oakland, California.) The history of Mrs. H, aged twenty-three years, as well as it could be obtained, brought out the fact that she had been markedly edematous and had had headaches and a scanty urinary output for several weeks past. At 5 P.M. of November 14, 1911, she gave birth to her first and living child. At 9 she had a convulsion that lasted fifteen minutes, and four more occurred in the night. She became unconscious. At 7 the next morning she was removed to the hospital. A severe convulsion occurred in the ambulance, and five more before 7.30 that evening. The patient vomited several times, the pulse ranged between 140 and 160, the respiration was 36, and the unconsciousness continued. In these twenty-seven and one-half hours she was effectively sweated several times, two magnesium sulphate and glycerine enemas were given, and two liters of 0.85 per cent. sodium chloride solution were given subcutaneously; 210 c.c. of bloody urine filled with albumin were obtained by catheter during these hours.

At this time two liters of the following solution was given intravenously:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Water, enough to make	1000 c.c.

An hour later an involuntary urination occurred, of which only 320 c.c. were caught; at 10.30 occurred a second, and at 11.30 a third. At 2.15 in the night the patient was rational for a few minutes, and at 8.30 A.M. she awakened completely. Through the day she was given 1000 c.c. of the above formula by slow drip into the rectum, and water by mouth ad libitum. The total urinary output in this twenty-four hour period was 3968 c.c., and except for the first specimens which were bloody, the urine was fairly clear, intensely acid, and filled with albumin and casts of all kinds. The pulse which at the time of the intravenous injection was

140, rose to 150 after the injection, to fall gradually to 102 by the next morning.

In the next twenty-four hour period the injection by rectum of the alkaline hypertonic sodium chloride solution was continued, about 300 c.c. being injected and retained every six hours. Alkaline water by mouth was freely urged day and night. At 8 A.M. of November 17 the urine was neutral for the first time, and of a clear amber color. The total urinary output for this twenty-four hour period was 3300 c.c., with considerable albumin still present.

The history of the next five days is indicated in the following summary:

Date.	Temperature.	Pulse.	Respiration.	Urine in 24 hours.	Character.	Remarks.
Nov. 18	99.4°–97.8°	104–84	24–20	3840+	Dark amber to clear. Neutral, no albumin.	600 c.c. alkaline hypertonic salt solution by rectum. Glass of alkaline water every half hour, day and night, by mouth.
Nov. 19	99.8°–97.8°	108–92	20	5216	Clear, neutral, no albumin.	Edema of limbs subsiding. Solid food allowed. Alkali by mouth only.
Nov. 20	99.8°–97.4°	108–88	20	3552+	Clear, neutral, no albumin.	Edema of limbs subsiding. Solid food allowed. Alkali by mouth only.
Nov. 21	99.8°–97.8°	112–88	20	3840	Clear, neutral, no albumin.	Edema noticeable in flanks only. Gone from rest of body. Alkali by mouth only. On light general diet.
Nov. 22	98.4°–98.0°	100–80	20	3600	Clear, neutral, no albumin.	Edema entirely gone.

From this time on until her discharge from the hospital, December 5, her history was uneventful. Her diet was unrestricted except that alkali was added to her drinking water, given both day and night, and she was urged to salt her food.

CASE VI.—(Dr. N. A. Hamilton, Franklin, Ohio.) During the last week of her pregnancy, Mrs. M., aged twenty-nine years, had edema of the legs, and suffered from impairment of vision to the extent of not being able to recognize her friends on the street. Her urine during this period was not brought to her physician for examination, though previous examinations had been negative. At term, on March 24, she went into labor, and was delivered normally of a living child by Dr. S. S. Stahl. The delivery occurred rapidly. The patient made normal progress until the fourth day (March 27), when she developed a temperature of 102° F., with a pulse of 110. This was attributed to an infection of the parturient

canal. At the same time she became markedly nervous, complained of headache, and had great roaring in the ears. The urine became very scanty, and heavily loaded with albumin and casts. This condition continued until March 31. On this day the pain in the head became very severe, nausea and vomiting occurred, and a marked numbness of the right arm and leg developed. The patient was pale and generally edematous. There was a twitching of the muscles in various parts of the body. At noon on this day an active administration of sodium carbonate and sodium chloride by mouth (0.33 gram each, every hour, with half glass of water) was started, and on the succeeding day this was given in the following form by rectum:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

In the twenty-four hours during which the sodium chloride and sodium carbonate were given by mouth, the patient's condition improved only slightly. On the following day, when administration by rectum was commenced, a rapid clearing began. The patient's history is summarized in the following table.

24-hour period ending	Highest pulse.	Highest temperature.	Urine.	Medication.	Remarks.
April 1	110	102.0°	720	Salt and alkali by mouth.	Signs and symptoms as above. General twitching. Much albumin.
April 2	115	102.2°	3420	Salt and alkali by rectum.	General symptoms better. Albumin less.
April 3	100	101.0°	2730	Salt and alkali by rectum.	Patient comfortable; no headache, nausea, or vomiting. Edema less. Albumin very much less in amount.
April 4	80	101.0°	3060	Rectal administration stopped. Alkali and salt by mouth only.	Same. Edema lessening. Albumin in traces only.
April 5	78	101.3°	2700	Salt and alkali by mouth only.	Traces of albumin only.
April 6	84	101.1°	1680	Salt and alkali by mouth only.	No albumin or casts.
April 7	84	100.4°	1110	Salt and alkali by mouth only.	No albumin or casts.
April 8	80	100.4°	1530	Salt and alkali by mouth only.	No albumin or casts.
April 9	78	100.1°	1500	Salt and alkali by mouth only.	All edema gone; patient feels entirely well. No albumin or casts.

The temperature continued a few days longer, but otherwise the patient went on to an uninterrupted recovery.

Case VII.—(Dr. Carl E. Curdts, Oakland, California.) Mrs. A. B. J., aged twenty-three years, entered the hospital, practically at term, in the early morning of July 14, 1912. She had always been well, and up to the eighth month of this her first pregnancy had noted nothing abnormal. At this time her feet began to swell and her face became puffy, and some albumin and casts were found in her urine. In the ten days before entering the hospital she had been on a milk diet, and largely in bed. Nevertheless, she had grown progressively worse, her edema becoming general and marked, and her urinary secretion dropping to "less than a pint measure" a day. Headache in the last two days had been constant. Her eyesight had been failing for a week past so that on admission she could only distinguish light from darkness with her left eye, and with her right she could only recognize gross objects at a distance. In the last day before coming to the hospital, and during the morning at the hospital she complained of "twitching and nervousness."

At noon of her first day in the hospital she passed 90 c.c. of urine—the first since the night before, according to her statement. This urine was deep amber, rather syrupy, and acid to paranitrophenol. On boiling with acetic acid the urine set into a solid jelly. An Esbach determination, using citric-picric acid as the reagent, showed 14 grams of albumin to the liter. The urine was filled with casts, mainly hyaline. The patient's pulse was 102, her temperature normal.

While immediate delivery by vaginal Cæsarean section had been recommended, it was felt, for reasons to be discussed later, that no such immediate haste was necessary. She was, in consequence, given the following formula by slow drip into the rectum:

Sodium catbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water	1000 c.c.

She took the drip well, and in the course of the afternoon absorbed and retained 720 c.c. At 3.30 P.M. she voided 378 c.c. of urine; at 6.45, 300 c.c.; at 8.55, 90 c.c.; and at midnight 315 c.c. The patient's pulse gradually fell to 82 by 5.30, and remained here. At the same time she volunteered that her headache was much improved, and that she could see more clearly. In the night of July 15 she was given 420 c.c. more of the solution by rectum. At 2.30 A.M. she voided 150 c.c. of urine; at 4, 60 c.c.; at 8.30, 120 c.c.; at 10.20, 60 c.c., and at noon, 63 c.c. The total urine for these first twenty-four hours in which the alkaline hypertonic sodium chloride solution was given was, therefore, 1536 c.c. In spite of the disturbance incident to giving her the solution, the patient insisted this morning that her headache was almost gone, that here eyesight had greatly improved, and that she felt more comfortable than for several

days past. The urine had gradually decreased in acidity, so that the second specimen obtained after starting the drip was neutral to litmus. The Esbach determination showed a drop to 7.5 and 6.5 grams of albumin to the liter. The later specimens of urine clearly indicated that a higher salt concentration was prevailing in the body because the albumin on boiling with a drop of acetic acid no longer jellied, but was precipitated in flocculent masses.

In the early afternoon of July 15 the patient experienced some uterine pains, which gradually became more severe. On account of the pains rectal injections had to be stopped. The patient was given as a substitute 8 grams of sodium citrate by mouth in several small doses. At 7.30 P.M. the pains became very severe and frequent, and at 11.30 she delivered herself of a healthy, living, male child. Ether was administered, and forceps were used to accelerate labor after the head appeared at the vulva. After the pains had continued several hours the patient's headache increased, but otherwise she continued to feel well. The pulse rose from 82, when the first labor pains were felt, to 102 between the pains, when delivery was in actual progress. Up to the time of delivery she passed 270 c.c. of urine, and at 10.30 the next morning 340 c.c. were obtained by catheter. Both these specimens were dark amber, intensely acid to methyl red, and barely alkaline to paranitrophenol, gave a heavy curdy precipitate on boiling with acetic acid, and showed 15 grams of albumin to the liter (Esbach). Every field of a centrifuged specimen contained dozens of hyaline and finely granular casts. At this time headache was slight, her eyesight more blurred than before labor, her temperature normal, and her pulse 88.

At noon of this day, July 16, she was again started on the alkaline hypertonic sodium chloride solution, and in the course of the afternoon absorbed 570 c.c. At 4.15 she was catheterized and 690 c.c. of urine were found, and at 11 P.M. another 780 c.c. were obtained. The first of these specimens was paler than previous specimens, was still decidedly acid to litmus and methyl red, and contained 5 grams of albumin to the liter. Many granular and hyaline casts and red and white blood corpuscles could be found in the sedimented urine. The second specimen was alkaline to methyl red and neutral to litmus and the Esbach determination showed 2.25 grams of albumin to the liter. Only isolated casts could be found in the centrifuged specimen. The patient was now given 2 grams of sodium citrate by mouth every four hours, and milk and lime water every two hours. Through the night and up to noon of July 17 she passed 1770 c.c., making a total for this twenty-four hour period of 3240 c.c. This night and morning urine was clear, neutral to litmus, alkaline to methyl red, showed a few granular and hyaline casts, and contained 1.75 grams albumin to the liter. The patient slept fairly well, said her headache was almost

gone, and that she could again recognize the details of her surroundings. At noon she had no headache, could read the smaller letters of a newspaper, and showed a decided decrease in her general edema.

She was now given an unrestricted diet, to which she was urged to add plenty of table salt. Vichy water was urged upon her, to which several grams of sodium citrate were added. To the milk which she consumed lime water was added. Her history is summarized in the following table:

For 24-hour period ending at noon.	Total urine.	Grams albumin per liter (Esbach).	Remarks.
July 18	3280	2.0	Unrestricted diet, Vichy water, milk with lime water and 8 grams of sodium citrate per 24 hours. Some casts and white blood cells.
July 19	2520+	2.0	Unrestricted diet, Vichy water, milk with lime water and 8 grams of sodium citrate per 24 hours. No general edema visible. Eyes slightly puffy. Good appetite. Feels well.
July 20	2366+	2.5	Unrestricted diet, Vichy water, milk with lime water and 8 grams of sodium citrate per 24 hours.
	contaminated with lochia.	One specimen only.	All signs of edema gone. Only occasional cast in centrifuged specimen. Some red and white blood corpuscles. Urine neutral. The albumin does not precipitate easily on boiling.
July 21	3000+	1.7	No casts. Diet, Vichy water, etc. Sodium citrate stopped and 0.7 gram of calcium chloride every 2 hours day and night substituted for it. Urine faintly alkaline. Albumin comes down readily on boiling with acetic acid. Pulse, 78; temperature normal.
July 22	2300+	1.0	No casts. Diet, Vichy water, etc., as yesterday.
July 23	2250+	Trace	No casts.
July 24	1980+	Trace	No casts. Calcium discontinued.
July 25	2400+	0	Urine negative.
July 26	2136+	0	Urine negative.
July 29	2346	0	Urine negative. Left hospital.

At the present writing this patient is entirely well.

We move from the protracted case of nephritis which is the result of a lasting intoxication of some kind by imperceptible steps over into the chronic nephritides. But as soon as we discuss the chronic nephritides we find that we have to distinguish between those which represent a mere continuation of what was once a more acute process (the chronic parenchymatous nephritides, the the secondarily contracted kidneys) and those which are chronic

from the start as in the type generally known as chronic interstitial nephritis (primarily contracted kidney) associated with changes in the cardiovascular system. Very evidently, if our views are accepted, the nephritis which continues because of a protracted intoxication needs to be treated with alkali, salt, and water in an equally protracted way. It has seemed to me that such a procedure yields good, and at times unexpectedly good results, but I refrain from a detailed recital of such cases, for it is impossible, except as one works these things out for himself, to adequately meet the eternal argument that what has happened in such cases would have happened anyway.

Especially is it difficult to meet such an argument when we deal with the chronic interstitial types of nephritis with their associated cardiovascular disease. One can from the start foresee that this type of nephritis offers the least possible chance of being markedly benefited by an alkali-salt-water therapy, and in its final stages none at all. I have emphasized this repeatedly, and were it not for the fact that it is upon this very type of case that some of my critics have based their arguments, it would scarcely be necessary to again refer to some self-evident facts. How much and what can we do for such cases?

The primary change in chronic interstitial nephritis associated with vascular disease is not nephritis but vascular disease. Every experimental fact and all physiological reasoning bears this out.[1] In consequence of the vascular disease one piece after another of the kidney suffers destruction. These pieces as they degenerate show the morphological evidences of "parenchymatous nephritis," and corresponding with these destructive lesions we find traces of albumin and a few casts in the urine. This process may go on for years without being noticed by the patient, for the healthy kidney (we can easily get along with one-fourth our total kidney substance) between his areas of nephritis is able to carry on the necessary functions of excretion. Such a patient is more likely to be first made aware of his condition in a life insurance office than in that of a physician whom he has himself sought. And if we make

[1] For a discussion see Martin H. Fischer, Edema, 192, New York, 1910; Nephritis, 56 and 94, New York, 1912.

the diagnosis for him, his blood pressure and the visible changes in his heart and bloodvessels are what lead us to a correct estimate of the significance of his albumin and casts.

If we but remember that the bloodvessel disease is the primary thing, then we get also a correct estimate of the significance of the changes in distant organs which men are in the habit of considering consequences of chronic interstitial nephritis. An "albuminuric retinitis," a glaucoma, persistent headaches, even the uremic convulsions and coma occurring in these cases are the same thing in the retina, the eye, or the brain which in the kidney we call chronic nephritis. The hemorrhage into and swelling of the retina, the swelling of the eye with its clouding of the clear media, the edema of the brain represent in these organs the equivalent of the hemorrhage, the clouding, and the swelling of smaller or larger areas of the kidney affected with chronic interstitial nephritis, and that which is common to both is disease of the bloodvessels. *And as this bloodvessel disease cannot be and is not materially influenced by the injection of alkali, salt, and water, so also can this therapeutic procedure be of little or no use in this type of disease. The only cases in which it can be of service are those in which the bloodvessel disease is in itself not wholly responsible for the observed changes, but where other temporarily active factors have been or are also responsible in bringing about our clinical picture.*

An illustration of this is offered in Case II outlined above. Here to the picture of an established chronic interstitial nephritis associated with cardiovascular disease, was added an intoxication with an anesthetic. The exacerbation is represented by the effects of the anesthetic upon the kidney, which effects are added to those already produced in this organ by the irremovable bloodvessel disease. Cold, hard muscular work, an infection, or an alcoholic spree might have done what the ether did. And the alkali, salt, and water would have relieved the consequences of such added factors equally well; but bloodvessel changes that permanently interfere with the blood supply to a portion or all of an organ, especially when we deal with end-arteries, are not relievable by any such schemes.

Perhaps these ideas may be yet better illustrated if we introduce

the following abstract of the clinical history of a glaucomatous attack. As we have repeatedly pointed out, glaucoma is in the eye what we call nephritis in the kidney.[1]

CASE VIII.—(Dr. Hayward G. Thomas, Oakland, California.) Mr. F. C., aged seventy-two years, goes to his office daily. He has for fifteen years had some albumin and casts in his urine. Unless his carbohydrates are consumed in moderation, he also has sugar. All his superficial arteries are easily palpable and tortuous, and his heart is hypertrophied, especially to the left. The second heart sound is accentuated. His blood pressure is constantly 190, and rises to 210 mm. of mercury. He has never had a generalized edema.

On July 16, after a day of mental and physical fatigue, he developed pain in his left eye and left temple, noticed that his eye was "bloodshot," and that he could not see the outline of objects clearly. The condition continued through the night, the pain being so severe as to keep him awake. In the morning of July 17 his state had not improved, and his eyesight had fallen off still more. He tolerated his condition throughout this day, and through the succeeding night and day, by which time he declared himself completely blind in the affected eye.

In the middle of the afternoon of July 18 he summoned Dr. Thomas, who found the eye hard (tension +3), pupil dilated to size 5, Morton scale, conjunctiva very much chemosed, cornea slightly steamy—a typical attack of the so-called "acute inflammatory glaucoma." Instillations of eserine were at once begun, and the patient moved to the hospital. The instillations were entirely without effect.

At 9 P.M. a slow injection of the following solution into the rectum was started:

Sodium carbonate (monohydrated, $Na_2CO_3.H_2O$)	4.3 grams
Sodium chloride	14.0 grams
Distilled water, enough to make	1000 c.c.

The patient retained the solution well, and by midnight had taken up the whole liter. The tension in the eye had fallen appreciably an hour after the injection was started, and at midnight was normal to the touch. At the same time the subjective symptoms of the patient improved, and he went to sleep. At 4 A.M., 500 c.c. more of the above formula were injected and retained. At daybreak the patient was able to recognize gross objects, and through the day his vision became steadily clearer.

[1] See Martin H. Fischer, Trans. Amer. Acad. Ophth., Otolaryn., 1911, 193, where references to earlier papers on this subject will be found.

He remained under observation in the hospital for two days longer. No new symptoms developed, and he was discharged with completely restored vision.

Prompt as is the relief of tension with its various associated symptoms in such a case as we have just described, our therapeutic procedure does not in any sense constitute a "cure," as I have so often emphasized. In the case just detailed I hold that vascular disease was primarily responsible for a diminished oxygen supply to the eye. For years such a change had led to no appreciable symptoms so far as the eye was concerned, but one day in consequence of unusual muscular and mental fatigue, aided possibly by an "acidosis" incident to his sugar intolerance, the acid accumulation from these sources added to that initially incident to the bad blood supply to the eye, sufficed to so materially increase the hydration capacity of his ocular colloids that they swelled to the point of giving him easily recognized signs and symptoms—a frank edema of the eyeball, a glaucomatous attack. But the reduction of this attack did not change his bloodvessel disease, and so it could safely be predicted that in consequence of another period of hard work or dietary indiscretions he would again get eye symptoms.

As a matter of fact, Dr. Thomas reports that after two months of freedom from symptoms the patient tired of his restricted activities, and his alkalinized diet and had two more attacks of increased tension though not of a severe type. The first of these was controlled by the same eserine solution which in the initial severe attack had been unable to reduce the tension. In the second of these milder attacks the eserine again proved unavailing, even though a contraction of the pupil resulted. An active administration by mouth of alkali and table salt with water was turned to, and while using this the tension returned to normal.

That which we have said here regarding glaucoma holds with equal force for the kidney, and this whether the vascular changes under discussion involve only microscopic areas in the kidney or larger areas up to the entire organ.

If the simple argument that I have outlined will be borne in

mind it will help to lead to a better understanding of what may be and what cannot be expected from the use of alkali, salt, and water in the chronic types of nephritis. Incidentally we can also see what may be accomplished for the edema, whether involving an individual organ or the whole body, in any case of heart disease. The final picture of a chronic interstitial nephritis is half the time not that of a pure nephritis, but one of this plus a failing heart. Only too often is the last insult administered to a remaining nubbin of kidney that for years maybe has served to keep a patient alive, by the cardiac muscle giving way (with a resulting generalized lack of oxygen, abnormal acid production and accumulation in all the tissues of the body, and so an edema). When a heart, from any cause whatsoever, drops below the lowest level of an efficiency necessary to maintain a proper circulation, and has no remnants of recuperative powers left in it, alkali and salt cannot supply them.[1]

The succeeding Cases IX and X will illustrate the application of an alkali and salt therapy to clinical conditions which are, in general, regarded as consequences of an intercurrent "nephritis." To us they seem rather to illustrate the essential sameness that exists between that which in the kidney is called nephritis and that which in other organs goes by such special pathological or clinical names as cloudy swelling, stupor, coma, etc.; and as we found alkali and salts of service in the former, it will not surprise us to find them of service in the latter also.

Case IX.—(Drs. Charles G. Pieck and E. M. Baehr, Cincinnati, Ohio.) The patient, E. E., aged six years, had scarlet fever on May 19, 1912. The attack was characterized by an intense eruption, but relatively little fever, and no evident throat complications. He was up and around in

[1] This is the type of case chosen by Joseph L. Miller (Amer. Jour. Med. Sci., 1912, cxliv, 8; Jour. Amer. Med. Assoc., 1912, lviii, 1972) upon which to test out the value of a salt-alkali therapy. Aside from the fact that his "'Fisher' solution" has a composition all his own, his results were entirely predictable. According to his own statement the majority of his cases were nephritics with permanently decompensated hearts. Naturally alkali and salt could not produce a diuresis where the mechanism for water secretion was about gone. Only heart tonics such as caffein and its derivatives, drugs, in other words, which gave these hearts a last kick (and therefore assured a temporarily better oxygen supply to the kidney and body tissues generally), gave a temporary "diuresis." It was not necessary to be a believer in any of the colloidal notions of water absorption to foresee all this, for we have known since 1860 that an inadequate circulation will not allow even a normal kidney to secrete urine.

less than a week. Twelve days later his mother called his physician because the boy had begun to complain of pain and distress in the throat. There was found an enlargement of the cervical glands, but nothing in the mouth or pharynx. The child grew worse during the week, became dull and listless, had no desire to eat, and was sleepy and feverish. His mother stated she knew the boy had not been passing a normal quantity of urine during this period.

This condition persisted for two weeks, the child growing more and more listless until he was in a continuous state of lethargy. He was asleep most of the time and had to be aroused to eat. Only upon becoming aware that his feet had become swollen did the mother call the physician a second time. At the time of his visit he found the child in a deep stupor with marked swelling of the face and feet. Slight convulsive manifestations were apparent.

On the morning of June 25, almost one month, therefore, after the onset of the condition, the child was given an intravenous injection of two liters of the following solution:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

No anesthetic was necessary for the child was comatose. The veins were not collapsed and the injection was given more rapidly than usual, requiring but fifteen minutes. The child's mental condition cleared rapidly, so that three hours after the injection he was able to recognize his surroundings and take water when asked to do so. In the following twenty-four hours after the injection he was made to drink two liters of pure water. His improvement continued steadily. In three days the edema had completely subsided, and the urine was flowing freely.

Samples of the urine obtained before the administration of the alkaline hypertonic salt solution were intensely acid and held albumin and casts in abundance. The urine obtained on the morning before the injection was begun showed casts as well as blood cells. Urine obtained a few hours after the treatment was alkaline and still contained albumin, but the casts had apparently disappeared. The mother stated that the child passed his urine on the morning following the injection after getting out of bed and securing the chamber himself.

The patient was kept in bed for four weeks, and the recovery was rapid and uninterrupted. The urine remained alkaline to methyl red during this entire period. Albumin persisted in every sample examined, but no casts could be found. The quantity of albumin was always less than 1 gram as measured by the Esbach method. At the present writing (October 22) the boy is entirely well generally, but still has a small amount of albumin in his urine.

Case X.—(Drs. G. M. Allen and E. M. Baehr, Cincinnati, Ohio.) The patient, W. S., was a boy, aged seven years, who had never before been ill. On December 10, 1911, his mother observed that he was ailing, tired, and listless. He complained of some distress in his neck below the left ear, where there could be felt an enlargement of the cervical glands. A low grade fever was present at this time. His throat and ears were examined but nothing unusual was discovered. This state of affairs continued until December 27, when his temperature rose to 103° F., and albumin and casts appeared in abundance in the urine.

The following is a brief synopsis of the development and course of the case:

From December 27 to January 3, 1912: The temperature ran an irregular course varying in intensity from 99° to 104° F. The average quantity of urine passed in twenty-four hours was 416 c.c. Albumin and casts persisted. During this period he was given per rectum an average of 500 c.c. of the following solution:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

To January 10: The fever persisted, but was lower than during the previous week, fluctuating between 99° and 102° F. He passed an average of 640 c.c. of urine daily. Albumin was constantly present, but was less in amount than before.

On January 10 there was a slight transitory delirium; there was also observed a thin watery discharge from the left ear. The administration of the alkaline hypertonic salt solution was continued as before.

To January 13: The temperature subsided gradually, reaching normal on January 12. The serous discharge from the ear continued. There was a leukocytosis of 34,000. On January 13, Dr. C. R. Holmes lanced the drums, but there was no pus found.

To January 17: The temperature remained normal on January 12, 13, and 14, and the urine free of albumin. The patient voided about 400 c.c. daily. At this time a slight edema of the face was seen, most pronounced under the eyes. His mental condition was quite good; on the morning of January 16 his mother read to him from his books, while he commented upon the pictures. That night without warning he developed a generalized convulsion which lasted two hours. The left side, apparently, was the worse involved.

Dr. Holmes opened the left mastoid bone that night, the child having been given chloroform as an anesthetic. No pus was found. A second convulsion, lighter than the first, occurred later in the night.

On the morning of January 17 the temperature was 103° F. The child

was in a stupor from which he could not be aroused except with difficulty. There were continued spasmodic twitchings of the left arm and hand, and it was noticed that he did not move these parts as he turned in his bed. The left leg as well was not moved as freely as the right. Urine was voided involuntarily. Albumin was present in considerable quantities.

At the request of Dr. Allen and Dr. Holt an intravenous injection was given by Dr. Baehr. One liter of the following solution was introduced into the superficial veins of the elbow:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

On account of the collapsed condition of the veins as well as the slight edema of the tissues, the veins could be found only by dissection. No anesthetic was required.

During the ensuing night the patient was given 1600 c.c. of water by mouth. In the course of the next twenty-four hours there were passed 1680 c.c. of urine. Except in the earliest specimens there was no albumin present even in traces. A blood examination made the morning after the injection showed a leukocytosis of 12,000.

To January 21: The child rallied a bit in the course of the next twenty-four hours, the pulse rate and vascular tone remained quite satisfactory, and the mental condition cleared a little. It could be discerned definitely at this time that there was a complete left-sided hemiplegia, the arm and the hand being more severely involved than the leg.

There was no fever, and the urine, for the most past, passed involuntarily, was of satisfactory quantity, and always free of albumin. On January 19 and 20 he began to become fretful and irritable, the edema of the face became more intense, and a suspicion was aroused that his vision had become impaired. On January 21 his general condition was bad, the pulse which had been of excellent quality during the entire illness now became very weak and rapid, and he slowly sank into a stupor which was practically a coma. His pupils responded feebly if at all to light stimulation, and Dr. Holmes believed he was able to discern a congestion of the retinal vessels, although no extravasation or edema of the disks was found.

After consultation a second intravenous injection of the alkaline solution was administered, this time in the right external jugular vein, as no other veins in the extremities could be located. Two liters were given. Chloroform was used as an anesthetic, chiefly to keep the child quiet during the operation. The coma seemed deep enough to allow of a much more severe manipulation. The entire time consumed was thirty minutes.

To January 30: In the first twenty-four hours he passed copious quantities of urine involuntarily. Water was given him to drink in large quantities, and milk alone was used for nourishment. Neither albumin nor casts were found at any time during this period. He was restless during the nights. His mental condition cleared rapidly. Three days after the injection a test of his vision was made. He was able to recognize his parents and the physicians about him.

Convalescence was slow though uninterrupted. Albumin never reappeared in the urine except upon one occasion when there was found a little circumscribed infection at the site of the first wound in the tissues of the elbow. As soon as proper drainage had been established the albumin disappeared.

The child had lost great weight and strength during these weeks, and the entire period of convalescence consisted in obtaining an improvement of these conditions. The paretic disturbance of the left arm and hand persisted, but showed a slight improvement from week to week.

During the following summer he was taken into the country about the Great Lakes, where he grew rapidly well. His father states that he left him there able to run about and paddle a canoe. The sole damage that remains evident is a tingling and stiffness in two fingers of the left hand.

Of a fair list of the acute nephritides with symptoms of an alarming character I have up to the present lost 3 cases. The first of these concerned an eclamptic woman, who, practically at term, threw herself out of bed in a convulsion early one morning. She was brought to the hospital late at night after the convulsion and coma had lasted through the day. No urine had been obtained since the night before, and catheterization was dry. She was injected intravenously with 1600 c.c. of an alkaline hypertonic salt solution at midnight. Her convulsions stopped, and she cleared mentally so that at 4 A.M. she talked to her nurse. Between midnight and 6 A.M. she passed 412 c.c. of urine filled with albumin and casts. She had no labor pains. At this time she was given ether and a vaginal Cæsarean section was performed. There was marked hemorrhage, and at 9 she died.

A second fatal case is reported as the following Case XI.

CASE XI.—(Dr. Elizabeth Campbell, Cincinnati, Ohio). Miss E. T., aged forty years, a school teacher, consulted her physician a month before entering the hospital because she was constantly tired. She was thin, but

without other physical findings of an abnormal nature. The urine was entirely negative. She was given an iron tonic, and urged to take a rest and to increase the amount of her food intake. On this regime her general health improved. February 24, 1912, she entered the hospital complaining of a sore throat which had developed two days previously. Both tonsils were found enlarged and inflamed, and the lymphatic glands on both sides of her neck were swollen and tender. She suffered from pains in various parts of her body, and was nauseated. Her pulse was 112, and her temperature varied between 99.2° in the morning and 101.6° F. in the early evening. Her urine on the first half day after her entrance amounted to 300 c.c., was dark amber, and acid, but free from albumin and casts. There was no edema. She was kept at complete rest in bed on a milk and vegetable diet.

By February 28 her throat had practically cleared, the neck glands had decreased in size, and her general symptoms had improved. During this time she had taken frequent 0.3 gram doses of sodium bicarbonate with 0.25 gram doses of aspirin. Her temperature now varied between 99°, in the morning and 100.6° F. in the evening. Her pulse ran between 96 and 112. On February 26 a trace of albumin was first noted in her highly acid urine as well as a few leukocytes. In the next two days the amount of albumin rose and granular, hyaline, and epithelial casts were noted. The urinary output per twenty-four hours was about 300 c.c. At the same time diacetic acid and acetone in abnormal amount appeared in it. Sugar was absent as before. During these days the patient was frequently nauseated, and a marked generalized edema developed.

From February 28 to March 7 the patient's temperature steadily declined so that on this day it was normal. Her pulse continued high, 104 to 120. Beginning on February 28, 480 c.c. of the following solution were administered daily by slow drip into the rectum:

Sodium carbonate ($Na_2CO_3.10H_2O$)	10 grams
Sodium chloride	14 grams
Distilled water, enough to make	1000 c.c.

The urinary output in twenty-four-hour periods after this regime was instituted ran as follows: 330+ c.c.; 480+ c.c.; 540+ c.c.; 725 c.c. 1080 c.c.; 1140 c.c.; 1050 c.c.; 1035+ c.c. The urine remained acid all the time that these injections were given, and acetone and diacetic acid continued to be present in abnormal quantities. The amount of albumin which in the first three days of this period had been great, diminished so that only a trace was noted in the later days. Medication during these days consisted of digitalin by hypodermic injection and occasional doses of strontium bromide at night.

On March 7, when I first saw the patient, her general condition was so good that I merely approved of the scheme of treatment that was being

followed out. The rectal injections of alkaline hypertonic salt solution were continued as before. The day previously the patient had been drowsy, nauseated, and had had headache, but at the time of my visit it was easier. That night she slept well. The following day she was uncomfortable because of an accumulation of gas in the bowels. Her temperature was normal and the pulse 108. Late this night and in the night she vomited though the rest of the night she slept fairly well. During these two twenty-four-hour periods 1140 and 1275 c.c. of acid urine were voided, containing only traces of albumin, very few granular casts, a few red and white blood corpuscles, and diacetic acid and acetone in excess.

The morning of March 9 was uneventful, but in the afternoon the patient began to complain of nausea. At 6 P.M. she vomited. The nausea and vomiting continued and became severe in the night. At 7 in the morning she complained of drowsiness; 1350 c.c. of urine were voided in this twenty-four-hour period.

At 7.30 A.M. (March 10) the patient was unable to swallow some proffered milk, and at 8 A.M. the nurse noted that the patient "had a far-away look in her eyes, and did not answer questions." Shortly afterward the breathing became labored. At 9.15 the nurse noted that the now unconscious patient looked constantly to the right, and at 9.30 a convulsion occurred. The convulsions were very severe and lasting, and chloroform was administered to control them. Crepitant and subcrepitant rales could be heard throughout the chest. Two 10-drop doses of tincture of veratrum viride were given into the muscles of the thigh.

At 12, with no feeling that anything could be accomplished thereby, 1500 c.c. of the alkaline hypertonic sodium chloride solution mentioned above were given intravenously. At 1.15, 300 c.c. of urine were taken from the bladder by catheter, at 2.15 another 235 c.c., and at 4.30 a final 75 c.c. The first of these specimens, which included all the urine which had accumulated in the bladder since midnight, was heavily loaded with albumin and casts. The second specimen contained relatively little albumin, the third again a large amount. All three specimens after the albumin had been removed reduced Fehling's solution heavily. The unconsciousness continued throughout the day, and the collection of fluid in her lungs increased. The patient could make no effort to cough it out, and the right to do a tracheotony and practice insufflation was denied. Slight muscular twitchings were noted, but no more convulsive seizures. Oxygen played into the mouth helped but little. At 6 P.M., heavily cyanotic, the patient died.

Autopsy performed immediately after death showed a well-marked edema of the superficial tissues. The peritoneal cavity was dry. The kidneys were somewhat swollen and of good color. The capsules stripped easily. The liver was smooth and somewhat swollen, the cut surface dry.

the spleen was swollen so that the capsule was tense, but otherwise showed no changes. The pleural cavities contained a few ounces of free fluid. The lungs, crepitated throughout, were heavy, and ran fluid from their cut surfaces. The apices showed some flat, thick scars in the pleura. The pericardial cavity was empty, the pericardium smooth. The heart muscle was flabby and slightly grayish. The endocardium was normal. Permission to open the head was not granted.

In retrospect I feel responsible for the loss of this woman. In spite of the daily rectal injections of alkali, it is clear she did not get enough, as evidenced by the persistence of an acid reaction in her urine and its content of diacetic acid and acetone. I erred further on the day of my first visit in not completely ignoring her good urinary output, and directing all attention to the well-marked brain symptoms evident the day before. As I have previously said, the state of one organ as evidenced by its function is not necessarily an index in these cases of the state of another. The alkali and salt should have been more industriously pushed on the day of my first visit, and subsequently.

The third case, to which Dr. E. M. Baehr took me, and which died, was in a young boy who for almost three weeks had suffered from a nose and throat infection with membrane formation which clinically looked like diphtheria, but which bacteriologically showed only streptococci. When we first saw the patient he had been anuric for four days, had a low grade fever, was pale, sleepy, and had a rapid thready pulse. The boy was in a state of "toxemic shock." We found a vein in the arm with difficulty, into which we injected a liter of alkaline hypertonic salt solution. We repeated this two days later, when the boy's general condition had not materially changed, and when we had the greatest difficulty in finding the thread-like, contracted jugular. The anuria was not relieved; we only obtained 30 c.c. of clear urine filled with albumin and casts on the day following our first injection—and with the symptoms of a gradually failing circulation the boy died on the fifth day after our initial visit.

A further recitation of cases could add little to that which we have already said. We did not start out to change, and are not even now interested in changing well-established therapeutic

measures. We only feel that if some of our colloid-chemical interpretations have been correctly made, some of these therapeutic measures will have to change, and along the lines we have suggested. The clinical results obtained especially in the acute cases and verified by the observations of a goodly number of objectively judging colleagues, would seem to bear us out, but we are not ignorant of how slippery is the ground of clinical obsercation. I mention these obvious truths because some of my critics think me unaware of them.

Surprise has at times been expressed at the quantity of fluid that is injected intravenously in clinical cases of nephritis and allied conditions. I have injected as high as four liters in twenty-four hours. Some clinicians have for various reasons remonstrated that this is dangerous, chiefly on mechanical grounds, and because this "throws work on the heart." In so far as the elimination of water from the body costs energy this is to a limited extent true, but only to a very limited extent as I have previously insisted. Physiologists know that the volume of circulating blood can be more than doubled without appreciable effect. Counting the blood in the human being as one thirteenth the body weight it is therefore entirely safe to inject a liter of fluid for every thirteen kilos of body weight. But, as we have pointed out elsewhere, this is a safe figure if blood, in other words water in combination with a colloid, is injected. Only such remains in the bloodvessels. When the water is injected "free," as in a salt solution, this rapidly leaves the bloodvessels, and so the amount of this that may be safely injected lies still higher. What we have said here is still largely true even when we deal with sclerosed bloodvessels, though to allow for the diminished elasticity of the bloodvessels in such cases a slower injection or injection of a less amount at more frequent intervals as the judgment of the operator may dictate may advantageously replace the single large injections.

About one in three of patients injected with alkaline hypertonic salt solution develop some reaction. At times they develop a chill which, however, does not last long, or they have a slight rise in temperature. Once I found sugar in the urine. It will be noticed that these findings are similar to those observed after intravenous

injections of "606" and other medicaments. European authors have laid stress on the distilled water employed in making up the solutions, maintaining that bacterial products are present in old distilled water. For this reason I have always urged the use of freshly distilled water, but even then I have seen these reactions. I next attributed the effect to the action of the alkali upon the red blood corpuscles and a resulting hemolysis. But this can only be a small part of it, for one of the worst reactions I ever saw occurred in a woman to whom I gave a concentrated solution of neutral salt only. To explain the findings, which are now being studied on laboratory animals, I have come to the tentative conclusion that two things are active: (1) We have a shrinking effect upon the red blood corpuscles which makes these less able to carry oxygen, and from this secondarily, and from the salt and alkali directly we also have; (2) and more important, an effect upon the medulla. This effect upon the medulla we think leads to the vasomotor effect in the skin which we call a chill, to the consequent retention of heat that accounts for the rise in temperature, and to the appearance of sugar in the urine, as C. Bock and F. A. Hoffmann[1] found many years ago when rabbits are profused with sodium chloride solutions. How to avoid these effects is not yet entirely clear to me. The rules that I have formulated for my own guidance call for the use of freshly distilled water and as slow an injection as is conveniently possible. It is undoubtedly better to give in place of a single large intravenous injection, several smaller ones separated by intervals of time which allow the salt and alkali to diffuse into the body tissues, but unfortunately the necessity of opening into more than one vein and the critical condition which we are usually asked to meet does not always allow of this. Before, throughout, and after the injection the patient is carefully protected from muscular exertion (if complete muscular and mental relaxation is not easily obtained, a *small* dose of codeine, heroin, or morphine may be used), and the possibility of a chill is guarded against by extra blankets, hot water bags, etc.

[1] Arch. f. (Anat. u.) Physiol., 1871, p. 550; Martin H. Fischer, University of California Publications in Physiology, 1903, i, 77; ibid., 1904, i, 87; Pflüger's Arch., 1904, cvi, 80; ibid., 1905, cix, 1.

The large number of clinical conditions involving so large a variety of organs in which an alkali and salt therapy proves of service may seem at first sight somewhat strange. Surprise will disappear if we will but remember that the observed changes are at all times a response to "injury." Whether such injury was induced by chemical, thermal, mechanical, or other means, the fact remains that practically every injury is associated with an abnormal production and accumulation of acid in the injured part, as is clearly manifested in the appearance after injury of the electrical change which we call the "current of injury." Most injuries to protoplasm are met by a reaction which in pathology is called "inflammation," a classic sign of which is, as we would expect, a "swelling" of the injured part, in other words, an edema.

V. CONCLUDING REMARKS

I have often been asked how, if my views regarding the value of increasing the salt intake in edema are correct, I explain the good results reported by Widal and his school when patients with edema are salt restricted. Paradoxical as seems the answer at first sight, I believe that in this scheme of treatment a salt concentration is also brought about but by indirect means. When the salt is taken out of the diet of a patient his appetite for water is tremendously decreased. If the patient is put upon the Carell dietary regime, care is taken from the start to assure not only a low salt intake, but a low water intake also. *It is this water restriction in both cases that to my mind produces the reduction in edema.*

We ordinarily overlook the fact that even under normal circumstances more than half the total water excretion is lost through the lungs and skin. Against the normal of, say, 1500 c.c. of water lost as urine, man loses 500 c.c. of water from his lungs, and 1000 to 2000 c.c. through his skin. If the patient is in a warm room, or if in addition he is warmly covered, as is so frequently the case with our nephritic, then these figures rise still higher. Even a completely anuric individual therefore suffers a substantial loss in weight if for any reason his water intake is restricted. But no

colloidal mass (whether this be a drying gelatine plate or a water-starved human being) loses its salt to the atmosphere as rapidly as it loses its water. The salts therefore become more concentrated in the cells and tissues of the body.

To understand what must be the effect of all this upon the body weight in general is not difficult. What a good effect it may have upon a nephritic kidney, a swelled brain, or any similar condition, can easily be realized when we consider the vicious circles that may and do become established in any of these organs or even in such an extremity as the leg or arm. I have repeatedly emphasized the fact that an edematous organ which is not given free play to swell tends to make itself progressively worse. As an organ swells, a hampering capsule, bony walls, or a small foramen make the swelling tissues compress the bloodvessels entering the affected organ, and so a lack of oxygen, in itself capable of producing an edema, is added to the already existing factors responsible for such an edema. For the reasons already stated, drink restriction or salt restriction, which to my mind leads to the same end, results in a drying out of the tissues of the body. If now a kidney in its process of swelling, say from an intoxication of some sort, has succeeded in rendering itself anuric by squeezing upon its blood supply, it is readily seen that a more normal state may once more be attained if we rob the body tissues and fluids of their water content, and so also draw upon the water content of the swollen kidney. The net result must be a better blood supply through the kidney, and if the initial insult to the kidney was not too severe or of too lasting a character, the restitution of a better circulation may well be equivalent to a relief of the kidney condition—just as when alkali and salt are gotten into this organ.

Then why not the water restriction-salt restriction scheme of therapy? I would answer that salt restriction constitutes an unnecessarily roundabout way, and a by no means pleasant one for all patients, to accomplish a water restriction which could as easily be obtained by direct means. Second, intoxication depends at all times upon concentration of the noxious agent. In a given case we can therefore dull the effects of an intoxicant only by

diluting it, and since we can guard ourselves against the bad effects of water by giving with this properly chosen salts in the right concentration, I have not been able to see the points of superiority of waiting for nature to dehydrate an organ which we can dehydrate as well and more rapidly, especially when in the former case we rob our patient of the added advantage of having water available with which to float off his poisonous products.

I would like to reëmphasize a last point in this entire matter of alkali, salt, and water therapy. Let us not forget that no solution is either absorbed or secreted as such, but that in every case the water and dissolved substances move independently of each other, at times in the same direction, at others in opposite directions, and usually at entirely different rates. A primary purpose in giving the hypertonic solutions that I have advised is to secure an increase in the salt concentration in the body. Now the body cells and fluids in any state associated with an edema have an increased capacity for holding water, and so water is more easily taken up by an edematous individual than by a normal one. *The edematous individual will therefore absorb water from any given salt solution more easily than will the normal individual.* A solution, "hypertonic" for a normal individual, may be "isotonic" for one whose colloids have an increased hydration capacity. So it need not surprise us when we find that when even a strongly hypertonic salt solution is given certain nephritics they show an initial increase in their edema. This only means that the colloids of their tissues were not previously saturated with water. Neither does it prove that the salt injected was responsible for this edema, but only that *the concentration of the salt which we succeeded in attaining in the body was not yet sufficiently high to decrease the existant high hydration capacity of the colloids of those tissues which showed the increased swelling. To remedy the situation we must give still more salt.* (And at this time, as at all other times when we are trying to increase the absolute salt concentration in the body, we must give with the salt as little water as possible.)

This paper must not be closed without the request that should its contents tempt any clinician to try the therapeutic methods here advocated, it tempt him also to study the considerations

upon which they are based.[1] It will prevent misunderstanding in criticism, and avoid the application of the suggested remedial measures to improperly chosen clinical cases.

Our original studies were made with an eye to analyzing in the terms of colloid chemistry a series of physiological and pathological phenomena which are associated with the problem of water absorp-

[1] Martin H. Fischer. The Physiology of Alimentation, New York, 1907, pp. 182–187 and 267–269.

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——— A Response to Some Criticisms of the Colloid-chemical Theory of Water Absorption by Protoplasm, Biochemical Bull., 1912, i, 444.

——— A Further Response to Some Criticisms of the Colloid-chemical Theory of Water Absorption by Protoplasm, Jour. Amer. Med. Assoc., 1912, lix, 1429.

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tion by the cells and fluids of the body, and with no immediate ideas of applying clinically any of our deductions. We think that we have succeeded in showing that the water of the body cells and fluids is carried as hydration water in combination with the hydrophilic, more especially the protein, colloids found in these. We have extended this to a definition of edema as a state in which the normal hydration capacity of the body colloids is increased. As causes of edema we have catalogued any substance or condition which is capable, under the circumstances existing in the body, of increasing the hydration capacity of a hydrophilic colloid. We have mentioned that an abnormal production or accumulation of acids constitutes one of these conditions, but in spite of its dominant role we have never maintained this to be the only one. As we discovered that all salts, including the neutral salts, decrease the hydration capacity of certain proteins swelling in the presence of an acid, it is but natural that we should have insisted that use of such a fact could and should be made in combating the increased hydration which in the body we call edema. And since such an edema, as it involves special cells, special organs, or the body as a whole, goes by many names, it is only natural and logical that we should have proposed the same principles for the treatment of all of them.

Upon such considerations, learned in the laboratory and upon animals where alone we can obtain strictly reproducible results, is based all that we have tried to formulate into some principles that should guide us in the treatment of all those clinical conditions in which an edema is a prominent feature, and independently of the fact whether this involves the whole body or individual organs like the skin, mucous membranes, kidney, brain, liver, eye, or optic nerve.

We do not believe that these fundamental propositions can be validly attacked. Progress may more profitably be sought by contribution to the chemical and physical analysis of the *mechanism* by which, in the simple cell, tissue, organ, or entire body, those conditions are brought about which alter the hydration capacity of their contained colloids. In this field first place will be taken on the side of metabolism by such studies as those of

W. M. Fletcher, F. G. Hopkins,[1] Ernst Weinland,[2] E. J. Lesser,[3] R. T. Woodyatt,[4] Samuel Amberg, and J. H. Mason Knox;[5] on the side of the more physical aspects of the problem by such studies as those of Raphael Ed. Liesegang,[6] who has shown how lipoid admixture prevents the diffusion of acid into and out of nervous tissue (thereby explaining why the ordinary acid intoxications do not so soon affect the brain as other organs, but how, if they have once done so, such intoxication cannot be as easily relieved here as in other organs), and of Wolfgang Ostwald,[7] who, in calling attention to the "synaeresis" exhibited by colloids explains how the heavily hydrated tissue colloids observed in edema must give off fluid, and so lead to the accumulations observed in the pleural, peritoneal, and other cavities of the body in pathological conditions associated with edema.

DISCUSSION

The President: During the last year or two there have appeared on this Continent two outstanding series of publications, curiously enough upon what are held to be contrasted yet allied subjects: That by Prof. Yandell Henderson upon shock and acapnia, and that by Prof. Martin Fischer upon edema and allied conditions; the former series laying stress upon the absence of carbonic acid as a cause of general disturbances, the other similarly laying stress upon excessive carbonic and other acids as the cause of another group of disorders. Both series are characterized by viewing well-known morbid states from a fresh standpoint, and both have from their originality aroused widespread interest and debate. Dr. Yandell Henderson has appealed more particularly to the surgeons; I have ventured to invite Dr. Fischer to address us. He will not, I feel assured, regard it as discourteous if, as hosts, we discuss the matter that he has presented to us; indeed, I know that he is prepared to be the subject of such a discussion. I would, on behalf of the Association, thank him for his very interesting and valuable contribution.

[1] Jour. Physiol., 1907, xxxv, 247.
[2] Many papers in Zeitschr. f. Biol. from xli on.
[3] Ergebnisse d. Physiol, 1909, viii, 742.
[4] Jour. Amer. Med. Assoc., 1910, lv, 2109.
[5] Ibid., 1912, lix, 1598.
[6] Ergebnisse d. Neurol. u. Psych., 1912, ii, 157.
[7] Personal communication.

Dr. T. C. Janeway: It is manifestly impossible to discuss such a matter as this in the time allotted, and we must all feel that Dr. Fischer has been at a great disadvantage in attempting to present in the space of twelve minutes so large a theory in a domain which has so long been the battleground of pathologists and clinicians. It seems to me obvious that we must begin with definitions and, like the theological discussions which go on forever over the use of words, that we should probably never agree unless we avoid misunderstandings in regard to our use of terms. It seems evident that Dr. Fischer, by the term nephritis, refers to the condition which many pathologists in this country today—notably Dr. Councilman and Dr. Mallory—decline to accept as nephritis at all, namely, the condition in which the entire histological change is confined to the tubular epithelium of the kidney. Dr. Fischer, neither in his book, nor here, considers the glomeruli either anatomically or physiologically important. The trend of modern pathological and clinical investigation is to lay a very large amount of stress on the condition of the glomeruli in any nephritis associated with the more serious symptoms of kidney disturbance. In experimental studies, too, the state of the vascular apparatus seems more significant than the changes in the cells of the tubules. When Dr. Fischer speaks of all the signs and symptoms of nephritis we must take issue with him because he includes only the changes in the tubular epithelium and functional changes which may easily be dependent upon these. We may speak of these as cloudy swelling, or we may speak of them as mild or simple nephritis, but under no conditions do we consider these tubular lesions as of predominant importance in producing the clinical picture of the disease.

As to matters of fact over and above this: so far as the histological picture is concerned, if one takes merely the tubular epithelium in the cases of subacute or subchronic nephritis variously spoken of as diffuse nephritis, parenchymatous nephritis, etc., in which there are definite histological changes in Bowman's capsule, changes in the bloodvessels of the tuft, exudate in the interstitial tissue, and so on, in varying combination, in this type there is one change of rather marked importance which Dr. Fischer has not duplicated in any way in his acid experiments, which clearly deserves consideration, namely, the presence of fat and fat of a peculiar kind in the tubular epithelium, the so-called anisotropic fat, showing evidence of cell degeneration.

When one comes to the problem of whether the kidney in nephritis is always acid, of course, it is somewhat rash to make positive statements. I cannot say that the study has been exhausted, and if one recommends the administration of alkali invariably, it is well to refer to recent studies of that subject which have come from clinics where the problem has been approached from the point of effect on albuminuria and cylindruria. Certainly one cannot dispute, if the theory is correct in the complete sense

in which Dr. Fischer claims it, that the administration of alkali ought to result at least in the albuminuria and cylindruria diminishing. I have been interested in trying the administration of alkalies, since von Hoesslin finds that the administration of alkali in some cases results in marked diminution of the albumin and casts and improvement in the excretion of water and sodium chloride. These cases bring it home to us that we must experiment along such lines. On the other hand, von Hoesslin found a considerable group of cases in which there was no effect on the albuminuria or cylindruria or on the water or salt output by alkalies, so that the infallibility of alkaline treatment as a therapeutic procedure can scarcely be maintained.

In the second place, Dr. Fischer makes the positive statement that the abstraction of sodium chloride from the diet of men or animals results in the occurrence of evidences of nephritis or of tubular epithelial degeneration in the urine. That is absolutely negatived by some very important experiments which were reported before this Association by Dr. Joslin some years ago on the effects of an ash-free diet. Dr. Joslin kept two men on an absolutely ash-free diet for about thirteen days with exhaustive analyses of their urine, and neither of them showed albumin or casts at any time, although they were starved of all mineral ingredients of the food, and this was carried to the most complete degree. Therefore, one can make no universal statements in regard to the effects of salt abstraction. It is much more important we should consider here, as practical clinicians, the therapeutic suggestions which Dr. Fischer has brought forward. His three points are the administration of alkali, the administration of sodium chloride, and the administration of large quantities of water as necessary to the treatment of all nephritis as he conceives it, that is the treatment of an acid-poisoned kidney. We may grant that. When one comes to apply these principles to the living patient one must admit that if he is to prove his points that the success of their application to what he would consider nephritis must be borne out by the universal testimony of competent observers. As to sodium chloride, there is no question that this is conspicuously lacking even in a type of kidney which may well fall into Dr. Fischer's category, namely, the kidney change which occurs in diabetics with severe acidosis. This should be the group *par excellence* for his treatment. Yet there is no group in existence in which the weight of the patient can be more strictly paralleled with the retention of sodium chloride. One can at any time add weight to these patients by the administration of sodium chloride and reduce it by abstraction. Now, however, this improvement by giving salt may work in Dr. Fischer's laboratory, it does not in patients, and clearly we must have other evidence than the evidence of the observer of fibrin in acid solution before we apply to patients principles of treatment which run absolutely counter to what any man may observe in hospital or office practice from

day to day. As to the administration of water, the indications are equally clear. The diseased kidney in what we all agree is nephritis may react very differently to the administration of sodium chloride and water in different patients and at different periods of the disease. Whether that is due to the changes in colloid constituents, at any rate, human beings afflicted with nephritis may react in quite different ways. There are certain cases of nephritis in which the administration of water in any way fails to evoke response. Anyone can observe it. I have been watching this in my wards for the last year. There is a considerable group of the more acute cases of nephritis in which there is marked impairment of water secretion, so that if you give water you increase their total tissue fluids and their visible edema, but not their urine. You may pour extra water into them and not one particle comes out. You may pour sodium chloride into them without any increase in the urinary chlorides. Then something takes place. At the end of the acute stage something takes place in the kidney which is associated with diuresis and increased sodium chloride output, and from that point on the maintenance of the salt-free diet and low water intake hurts them. Then you want to increase the water and salt. I think, as clinicians, our present endeavor should be to study these problems of nephritis, to study them in connection with the welfare of the patients, with careful quantitative control of the normal and abnormal substances excreted by the kidney, and not rush into the adoption of any universal theory or any universal panacea for what is probably a group of the most complex anatomical conditions and most complex functional disturbances which we know of in clinical medicine or pathology.

Dr. S. J. Meltzer: I take part in the discussion with some reluctance. I have great admiration for the gifts, the enthusiasm, and initiative of Dr. Fischer, and then I do not like to appear as an old fogy who frowns upon new, progressive, experimental work. However, it seems to me that it is rather in the interest of the proper progress of scientific medicine to protest against too sweeping claims. Dr. Fischer presents a view by which he claims to explain in a simple way the nature of all forms of edema, explains in a similar simple way the origin of all forms of nephritis, and on the basis of this view he has devised a remedy against nephritis which is, according to him, practically infallible, the few exceptional failures being due only to improper or untimely application of the remedy. One cannot help feeling that such sweeping assertions are not compatible with the proper handling of scientific problems. As a basis for his view Dr. Fischer offers essentially two experiments, one is that the addition of acid to a solution increases greatly the osmotic power of the latter, and the second is that the addition of sodium chloride neutralizes this action of acids. These interesting physico-chemical facts were brought forward

years ago by Jacques Loeb, in whose laboratory Dr. Fischer received his experimental training. Loeb himself attempted years ago to explain all forms of edema by the action of acids. In my lectures on edema I discussed the subject and wondered how this theory could ever explain pulmonary edema. But Loeb himself in collaboration with Beutner has recently shown that this action of acids applied only to dead and not to living tissues. I may also call attention to the authoritative criticism by Marchand of Fischer's theory. Now I do not wish to say that I know that Fischer's theories are wrong. All I wish to say is that in Fischer's method of scientific activity there is too little experimentation and by far too much generalization.

Dr. A. E. Taylor: I beg to be permitted to enter protest against the rather arbitrary criticism of Dr. Meltzer, which I believe goes beyond the substance of the situation. I believe it is the historical precedent that what is termed the progressive or the radical point of view, whatever its future, has usually to meet an extremely negative criticism, and I believe the data of this question as they are presented in the literature today merit a less widespread and exhaustive, categorically negative attitude than that which has been accorded to this general proposition by Dr. Meltzer. I beg to point out that the criticism of Marchand is based on a misapprehension. One point of Marchand is that the edema is not largely protoplastic, but intercellular; and apparently the supposition is that this state of affairs is averse to the interpretation of edema *per se* on the basis of a colloidal construction. This is a misapprehension if one takes the conception of colloidal advanced by Hardy. If this conception of Hardy's, which is a clear-cut one, is to be regarded as representing the fact it is as perfectly applicable to the plasma as to protoplasma, and must hold as clearly for blood serum as for protoplasm. Therefore the whole argument would apply to intercellular edema and the criticism of Marchand falls flat. As to salt reduction, I was the original subject on whom these experiments were conducted. I obtained in my own person effects which were not obtained in the men following my experiment. The point is true that so far as the men who followed me and myself were concerned we had no symptoms of nephritis. Dr. Moffitt, who is in the room, and who took care of me, will testify that there was nothing of that sort; and although there was a profound disturbance of the body due to salt abstraction, there were no symptoms of nephritis. This is not a final criticism; it is surprising how animals at times will resist salt abstraction, and it is possible –although Dr. Joslyn's experiment went far enough, that is, far enough to make me wish to go no farther— that if the experiment were continued over a longer period the patient might develop the renal lesions which might be due to salt abstraction.

Dr. L. F. Barker: I think that we will all agree that this paper and the discussion it has aroused have been entertaining and stimulating to thought. After all, interest and stimulus are among the principal functions of these meetings of ours. The normal progress of all disputes and controversies is from vagueness toward definiteness. It is obvious that this whole question of renal disease is in a state of great vagueness; indeed, the free use of the term nephritis here today shows how vague the subject is. Until we realize that "nephritis" and "renal disease" are not synonymous and coequal terms, we shall not get very far. It seems to me that accurate terminology is of considerable importance, that using, as far as possible, words which have a definite and easily ascertainable meaning, and using them carefully in the sense in which they should be used, we shall make progress faster.

The bringing forward of ideas based upon physical chemistry, in connection with renal disease, seems to me very desirable and useful. It is perhaps the first time such views, in connection with renal diseases, have been presented to this Association, and I believe that, as a result of what we have heard, we shall all think a little more about the physical-chemical side of problems in the future, and not confine our attention so exclusively as in the past to the bacteriological, pathological, and clinical sides.

Just a word more about "hypothesis." There is nothing more sterile than isolated, undisputed fact. If a fact that everyone accepts be brought before us it does not interest us long. The things that interest us most are the assertions that are half true, that some of us think are wholly true, and others of us believe are only partially true. These are the ideas that stimulate us to think, to analyze, to discuss, above all, to work. We will not work at things which are absolutely settled. What really helps us is the bringing forward of ideas that have some truth in them, ideas in which we are very much interested, and which appeal to us, but in which we may, ourselves, see some defect, and in which others may detect other errors. In such cases one has to "dig down to the untruth" which has appeared true to another. I hope that we shall never confine our discussions in this Association to isolated and fully accepted truths, for if we do, our discussions will have no vitality about them and will be a mere waste of time.

Dr. James Tyson: I should like to say a few words from a slightly different point of view. First, let me say that if Dr. Meltzer may claim old fogyism, I am sure I am still more an old fogy, and I beg you will excuse me, therefore, if what I say is not worth while. This paper has appeared to me very attractive, and has impressed me very strongly. In the matter of the therapeutic suggestions, take that of the administration of alkalies in the treatment of nephritis. In quite a long experience I have grown to adopt this as the very first measure, having in mind the

indication for diluent and diuretic effect; not that I am invariably successful, but this method has proved to be the least unsuccessful method in the treatment of these cases. Second, as to abstraction of chloride of sodium from the diet. In all the efforts I have made to determine whether abstraction of chloride of sodium reduces edema I have failed. This perhaps from lack of training in scientific accuracy. On the other hand, I am familiar with Dr. Fischer's book, and I have treated one case after his method and I am free to confess I failed. Like so many new measures it seemed at first as though it might prove useful, but failed.

Dr. Fischer: I do not think it necessary to quibble about the meaning of the term nephritis. I used it in its ordinary clinical sense as covering that symptom-complex familiar to everyone and characterized by the appearance of albumin and casts in the urine, by changes in the quantitative output of water and dissolved substances by the kidneys, by the appearance of edema, etc., in association with certain morphological changes in the kidneys themselves. The distinction between glomerular nephritis and other forms of nephritis has never appeared to me to be that distinct thing which some of our critics would have us to believe. Clinical observers accept as entirely proved the physiological teachings of half a century, that water is secreted by the glomeruli and dissolved substances by the tubules, and base sweeping deductions in pathological physiology upon these teachings of Bowman, Ludwig, and Heidenhain. I hope such a conception of urinary secretion is correct, but physiologists do not accept it with the faith that clinicians do. Conservatism compels one to accept but lightly any teaching which in its turn is based upon disputed scientific ground.

I have never tried to account for the fatty changes found in the kidney cells in certain types of nephritis, but they argue nothing against the general ideas I have been advancing. The abnormal appearance of fat in any degenerating cell is generally regarded as dependent upon a defective oxidation chemistry in the involved cell. The same suboxidation which, since Hoppe-Seyler and Araki's work, we have held to be responsible for the abnormal production of acid in cells can therefore be responsible for the abnormal production or accumulation of fat.

The question has been asked whether we really knew that the kidney is acid in nephritis. Dr. Janeway should define just what he means by his use of the term "acid." I speak always of an "abnormal production or accumulation of acid" in the kidney, and the evidence for such is too long to discuss here, but can be found in my book on nephritis. Such a abnormal production or accumulation of acid may occur in any tissue or organ to the point of killing it without evidencing itself to the litmus paper tests that are so frequently resorted to by way of proving me incorrect. In a series of nephritics in which I have observed the active

(hydrogen ion) acidity of the urine and of the blood by using graded indicators (with an eye to getting in this way on the basis of the laws of chemical equilibrium, an index of the acid-content of the kidney cells) I have found that the general symptoms of the nephritis increase and decrease as the acidity runs up or down. These findings will be published later.

Dr. Janeway and I can never settle here the question of whether salt restriction does a patient harm or does him good. If we are both reasonable men we must ultimately agree, but the best way in which to hasten such an agreement is not by debate but by mutual observation of the same case of nephritis.

Dr. Meltzer's criticisms have been largely met by Dr. Taylor, so I need not repeat. I would only like to say that in championing Marchand's criticism of my work on edema, Dr. Meltzer has probably chosen the weakest of all my critics, for Marchand understands but ill the relationship which exists between the explanation of biological phenomena in the terms of physiological nomenclature and the terms of physics and chemistry. I have little desire to enter into a personal discussion here where I am a guest, but perhaps I may be allowed to say this. I do not believe that anyone here, including Dr. Meltzer, has ever appreciated Jacques Loeb's ability and his services to medicine more keenly than I, and if Dr. Meltzer will take the trouble to look through my various papers on edema he will find that I have not only considered my illustrious teacher's contributions to this subject, but that I have referred to them and treated them in an extremely generous light. Certainly in so far as I was able I have tried to do this. Loeb has never contributed anything to the colloid-chemical notion of water absorption by protoplasm, but I have always insisted on the essential value of one of his experiments on edema, and this before and after Loeb himself had come to think so lightly of his edema paper that he did not republish it in his American collected papers, and Meltzer in his Harrington lectures on edema had dismissed Loeb's work as of no great importance.

In the limited time at my disposal here, both for my original remarks and the discussion, it has been impossible to go into details. Nearly every point which has been brought up here has been discussed in some of my writings. I have tried in these not to unnecessarily repeat myself, but even so they amount to a couple of books and twenty odd articles on this subject of water absorption by protoplasm. I do not blame my critics for not having had the courage to read them, but I must insist that should they read them much of their criticism would fall.

A FURTHER REPORT UPON THE NATURE AND MEDICAL TREATMENT OF GRAVES' DISEASE*

By S. P. BEEBE, M.D.
NEW YORK

DISCUSSION

Dr. George Dock: We have all become habituated to the idea that we are dealing with a hyperthyroidism. If nothing else had proved it surgical operations would. We can no longer question that taking away a lot of thyroid tissue from a so-called case of hyperthyroidism will produce a very different picture, but that does not disprove the possibility of there being another process there. There are other perversions of function which are so hypothetical that I almost hesitate to suggest them here, but diminished function should be remembered. The thought arises what causes the hypersecretion, and nothing would be more natural than to imagine that the patient had a hypo process first—hypersecretion secondarily. There are some clinical facts in the history of exophthalmic goitre which make us pause here. It is well known that some cases of exophthalmic goitre terminate in myxedema. May it not follow hypothyroidism? I do not mean well-marked ordinary myxedema, but it is an interesting fact that masked or incomplete myxedemas have certain symptoms common to exophthalmic goitre; one of them is rheumatism. Rheumatism has been described in all forms of hyperthyroidism. In myxedema loss of hair is often very characteristic in its localization in certain parts of the scalp, and in the eyebrows. That occurs in certain cases of Graves' disease. Walsh pointed this out in Graves' disease. I had a patient with a very marked exophthalmic goitre, and the previous history did not show anything very striking. He had marked rheumatic symptoms, in addition he had such a condition of his hair growth that when he was exposed only two or three times to x-rays on account of hyperplasia of the spleen, all the hair over his body disappeared, a condition that under ordinary exposure to x-rays hardly ever happens. In hyperthyroid patients

* This paper was read before the Association, but the manuscript was not received in time for publication.

it may easily happen. In going back far in our case books everyone of us can get histories that most of us would not pay attention to at the time of the patient's first coming to us. In the light of our later knowledge we can trace a probable relation to thyroid disease. Consider the cases with a history of nervous prostration or neurasthenia. In some of these muscular and psychic depression are extremely marked, and the treatment given them is apparently successful; but I have often wondered if these patients were not relieved of their nervous prostration by turning into hyperthyroid patients. Therefore, I would suggest looking into the early symptoms of hyperthyroidism for especially hypothyroid signs, usually in a mild form. Under the persuasive influence of Dr. Crile too much attention, I think, is being called to fright as a cause of hyperthyroidism. I do not know one case where that has been the active factor of the onset of the disease. For example, a woman who thinks she is poisoned, but had tachycardia before, can hardly be said to have had her heart disease caused by fright. Then a woman who has a thyroid operation performed, who comes partially from under the anesthetic on the table, finds herself covered with blood, goes to a glass and looks in and finds her eyes almost popping out of her orbital cavities, as in a case I know. Of course no one can imagine that such a patient did not have exophthalmic goitre before. If fright produces the disease, why don't we see exophthalmic goitre more often in women who have been attacked and attempts at rape perpetrated upon them; who have been robbed, or their houses entered? It might be very interesting for all of those who see women who have been frightened, or who have been in a condition where they might have been frightened, to follow them up and see whether they have any hyperthyroid symptoms afterward.

Dr. Louis B. Wilson: Many of the things which Dr. Beebe has said need no evidence. Dr. Beebe calls attention to the fact that he has not found confirmation of Kocher's definite statement that there is a hyperleukocytosis in these cases of hyperthyroidism. Since Kocher's first statement some years ago we have made a number of differential counts on about 800 cases of exophthalmic goitre and simple goitre as well. We have analyzed all the 27 deaths which have occurred in exophthalmic goitre, not one gave a high lymphocyte count. Of the 25 in which a high lymphocyte count was given, not one has been a severe case. It is true that in exophthalmic goitre there are a great many cases with a relatively high lymphocytosis up to 40 per cent., but it is equally true that in simple goitre we have equally high lymphocytosis. I am glad to hear Dr. Beebe affirm the fact brought out before that the symptoms are not due to the iodine that is in the gland, neither are the symptoms due to the secretion in the gland. If we are studying the effect of a factory on

a community we do not study the product alone. In studying the physiological effect of a gland we must study not only the manufacturing capacity, but its transportation facilities. That is the hypothesis on which we have proceeded for some time in our work. In case it be exophthalmic goitre in our clinic it has not shown hyperplasia, absolutely not. Furthermore, our clinicians have gotten to the point that they can diagnosticate a hyperplasia before operation in about 95 per cent. from the appearance of the patient. So far as results are concerned, all of our exophthalmic cases treated on January 1, 1910, were tabulated a year ago, and 71 per cent. of these people who were formerly a burden on themselves and friends, within three months of the operation have been able to return as working members of the community. This is practically the same as the results from the use of the serum.

Dr. Beebe: I do not wish to be understood as meaning that the disease is caused entirely by fright; but I am perfectly satisfied in my own mind that fright is a factor of considerable importance in the immediate development of acute symptoms in a person who has been in apparent good health.

I recall the case of a school teacher knocked down by a trolley-car in the city of New York. She had been examined for life insurance only a few days before and successfully passed. Within four days of the accident she developed the disease in the acute form. The gland increased in size after I first saw her, and the patient grew worse for a time. Another young woman was thrown out in a shallow lake, the boat was overturned, and although the water was only three or four feet deep, she floundered about for some time before she found it out. She had been in apparent good health up to this time. Immediately following this accident she developed an acute attack of hyperthyroidism. The fact that all people do not develop hyperthyroidism after fright is no argument against this point. Two persons exposed to the same degree of exposure would act quite differently—one may have an acute attack of rheumatism while the other may show a redevelopment of a chronic tuberculosis.

The fact that all persons do not respond to fright by development of hyperthyroidism does not mean that fright is not a factor of considerable importance. I believe I can safely say that in 20 per cent. of the acute cases which I have seen within the last two years fright was an important influence. Nervous disturbance due to worry or sickness in the family has likewise been an important factor.

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